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WO 2005/112633 A2

(54) **Title:** COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS

(57) **Abstract:** Compounds and compositions for the delivery of active agents are provided. Methods of administration and preparation are provided as well.

COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS

[1] This application claims the benefit of U.S. Provisional Application No. 60/576,088, filed June 1, 2004, U.S. Provisional Application No. 60/576,397, filed June 1, 2004, U.S. Provisional Application No. 60/576,105, filed June 1, 2004, U.S. Provisional Application No. 60/571,090, filed May 14, 2004, U.S. Provisional Application No. 60/571,092, filed May 14, 2004, U.S. Provisional Application No. 60/571,195, filed May 14, 2004, U.S. Provisional Application No. 60/571,194, filed May 14, 2004, U.S. Provisional Application No. 60/571,093, filed May 14, 2004, U.S. Provisional Application No. 60/571,055, filed May 14, 2004, U.S. Provisional Application No. 60/571,151, filed May 14, 2004, U.S. Provisional Application No. 60/571,315, filed May 14, 2004, U.S. Provisional Application No. 60/571,144, filed May 14, 2004, and U.S. Provisional Application 60/571,089, filed May 14, 2004, all of which are hereby incorporated by reference.

Field of the Invention

[2] The present invention relates to compounds and compositions for delivering active agents, such as biologically or chemically active agents, to a target. These compounds are well suited for forming non-covalent mixtures with active agents for oral and other routes of administration to animals. Methods for the preparation and administration of such compositions are also disclosed.

Background of the Invention

[3] Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, and/or the target itself. Biologically and chemically active agents are particularly vulnerable to such barriers.

[4] In the delivery to animals of biologically active and chemically active pharmacological and therapeutic agents, barriers are imposed by the body. Examples of physical barriers are the skin, epithelium, lipid bi-layers and various organ membranes that are relatively impermeable to certain active agents but must be traversed before reaching a target, such as the circulatory system. Chemical barriers include, but are not limited to, pH variations in the gastrointestinal (GI) tract and degrading enzymes.

[5] These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers. Among the numerous agents which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, such as mucopolysaccharides including, but not limited to, heparin; heparinoids; antibiotics; and other organic substances. These agents may be rapidly rendered ineffective or destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes, and the like. In addition, the size and structure of macromolecular drugs may prohibit absorption.

[6] Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of adjuvants (*e.g.*, resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of

enzymatic inhibitors (*e.g.*, pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. Liposomes have also been described as drug delivery systems for insulin and heparin. However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of adjuvants or inhibitors; (2) suitable low molecular weight cargos, i.e. active agents, are not available; (3) the systems exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

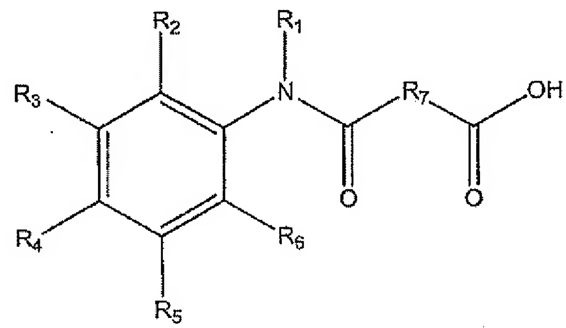
[7] Proteinoid microspheres have been used to deliver pharmaceuticals. See, for example, U.S. Patent Nos. 5,401,516; 5,443,841; and Re. 35,862. In addition, certain modified amino acids have been used to deliver pharmaceuticals. See, for example, U.S. Patent Nos. 5,629,020; 5,643,957; 5,766,633; 5,776,888; and 5,866,536, and International Patent Publication Nos., WO98/49135; WO00/06534; WO00/07979; WO00/40203; WO00/47188; WO00/50386; WO00/59863; WO01/32130, WO01/32596, WO01/44199, WO01/51454, WO02/02509, WO02/15959, WO02/16309, WO02/20466, WO02/19969, WO02/69937, WO03/45306.".

[8] More recently, a polymer has been conjugated to a modified amino acid or a derivative thereof via a linkage group to provide for polymeric delivery agents. The modified polymer may be any polymer, but preferred polymers include, but are not limited to, polyethylene glycol (PEG), and derivatives thereof. See, for example, International Patent Publication No. WO 00/40203.

However, there is still a need for simple, inexpensive delivery systems which are easily prepared and which can deliver a broad range of active agents by various routes.

Summary of the Invention

[9] The present invention provides compounds and compositions which facilitate the delivery of active agents. Delivery agent compounds of the present invention include compounds as shown below and pharmaceutically acceptable salts thereof:



Compound A

wherein:

R_1 is $-(CH_2)_m$-R_8, wherein m= 0 or 1;

R_2 - R_6 are independently selected from hydrogen, hydroxyl, halogen, C_1 - C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, and cyano;

R_7 is selected from C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, and C_2 - C_{10} alkynyl;

R_8 is selected from cyclopentyl, cyclohexyl and phenyl, wherein when R_8 is a phenyl, m=1; and

R_8 is optionally substituted with C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen or hydroxyl, or a combination thereof.

[10] In one embodiment, R^7 is C_1 alkyl.

[11] In another embodiment, R^7 is C_2 alkyl.

[12] In another embodiment, R^7 is a C_3 alkyl.

[13] In another embodiment, R^7 is a C_4 alkyl.

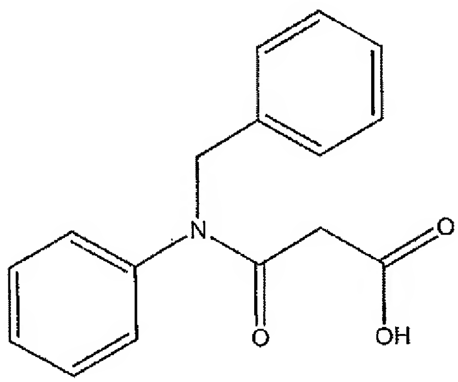
[14] In another embodiment, R^7 is a C_5 alkyl.

[15] In another embodiment, R^7 is a C_6 alkyl.

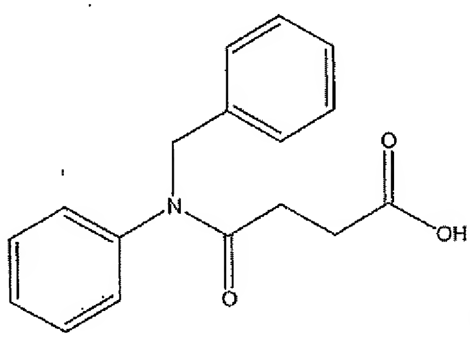
[16] In another embodiment, R^7 is a C_7 alkyl.

[17] In another embodiment, R^7 is a C_8 alkyl.

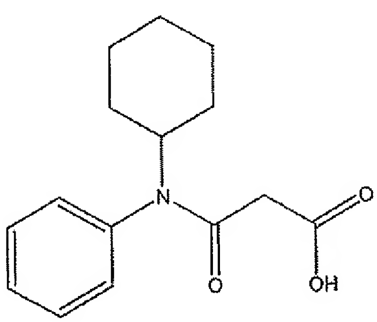
[18] Preferred compounds include, but are not limited to, the following compounds and pharmaceutically acceptable salts thereof:



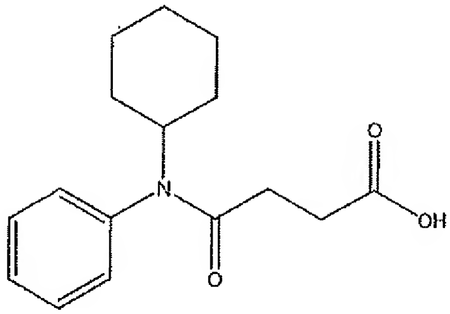
(Compound 1)



(Compound 2)



(Compound 3)



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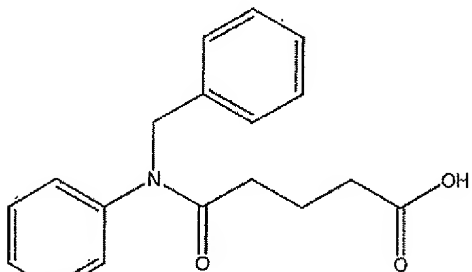

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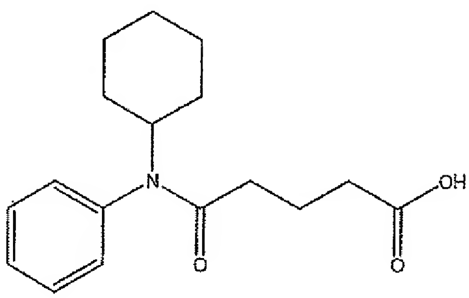

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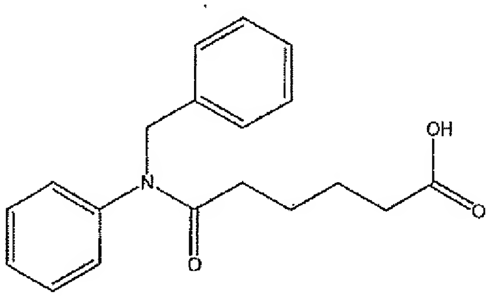

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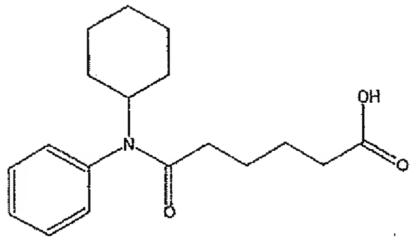

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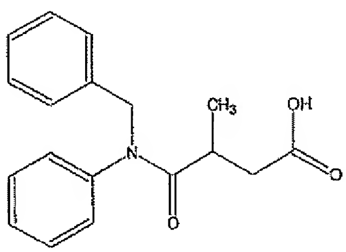

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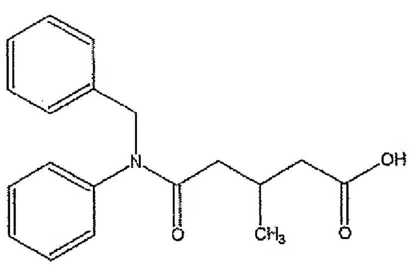

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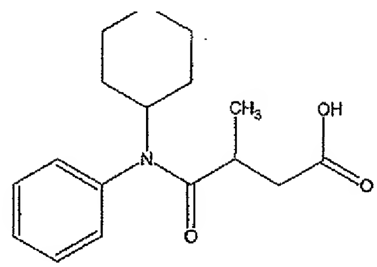
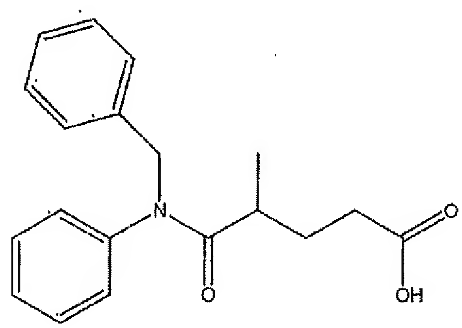
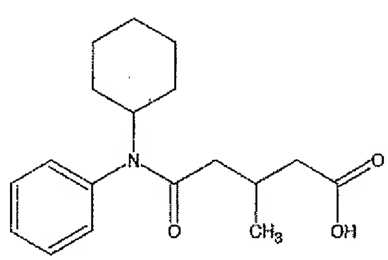


(Compound 11)



(Compound 12)



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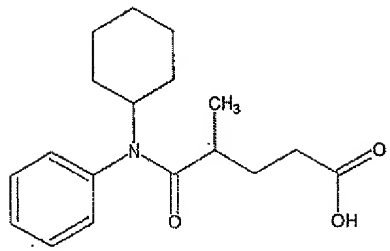

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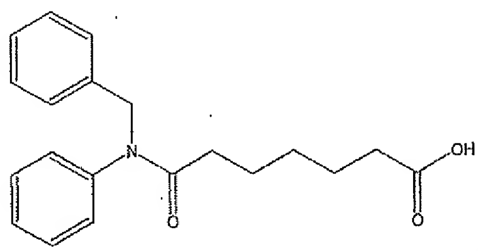

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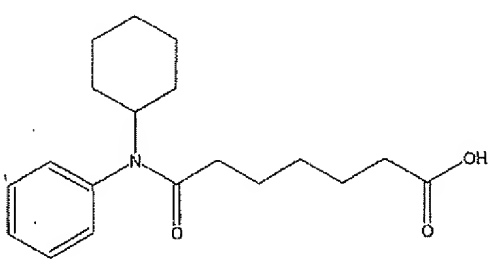
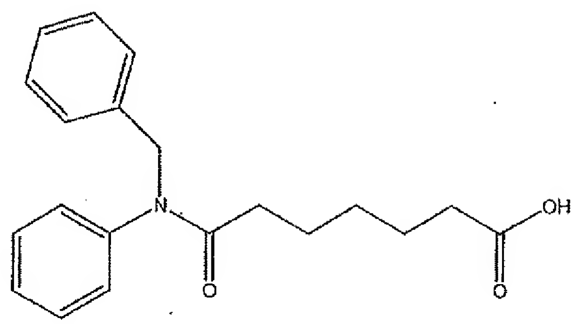


(Compound 16)



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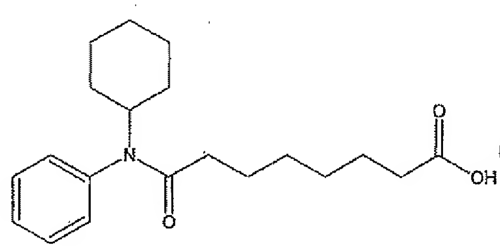

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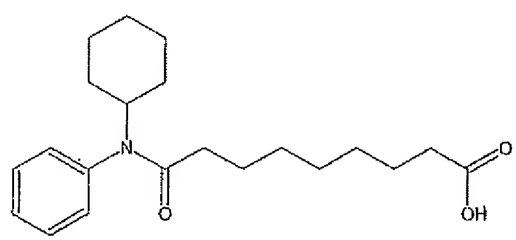

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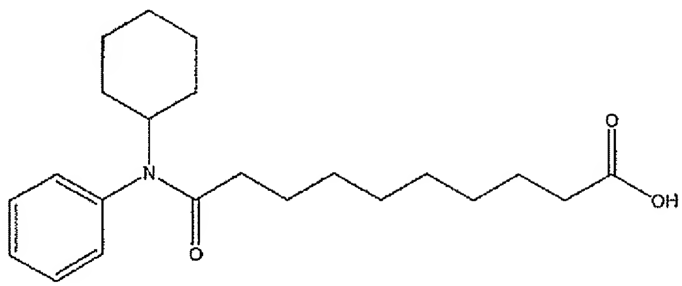

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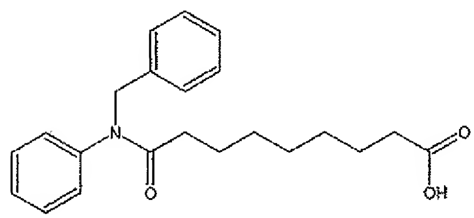

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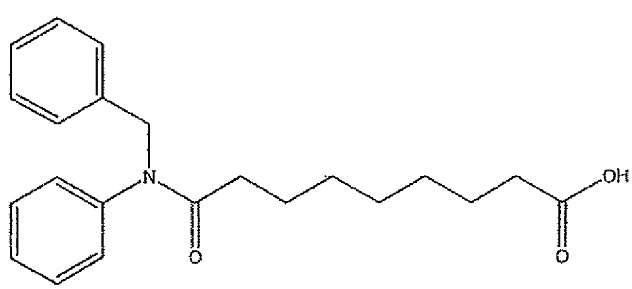
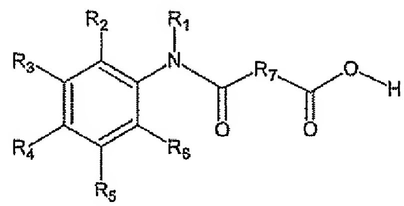


(Compound 22)

[19] Other delivery agent compounds of the present invention include those of the formula:



(Compound B)

and pharmaceutically acceptable salts thereof, wherein:

R_1 is a C_1 - C_6 alkyl, or C_2 - C_6 alkenyl,

R_2 - R_6 are independently chosen from the group consisting of hydrogen, hydroxyl, halogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2- C_4 alkynyl, C_1 - C_4 alkoxy, and cyano, and

R_7 is selected from the group consisting of C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, and C_2 - C_{10} alkynyl.

[20] In one embodiment, R2 – R6 independently are hydrogen, methyl, halogen, methoxy.

[21] In another embodiment, R2 – R6 independently are hydrogen, methyl, chlorine, methoxy.

[22] In another embodiment, R2 – R6 independently are hydrogen, methyl, flourine, methoxy.

[23] In another embodiment, R2 – R6 independently are hydrogen, methyl, iodine, methoxy.

[24] In another embodiment, R2 – R6 independently are hydrogen, methyl, bromine, methoxy.

[25] In another embodiment, R1 is C_1-C_3 alkyl.

[26] In another embodiment, R1 is a methyl.

[27] In another embodiment, R1 is an ethyl.

[28] In another embodiment, R1 is an isopropyl.

[29] In another embodiment, R2 is a methyl.

[30] In another embodiment, R2 is a halogen.

[31] In another embodiment, R2 is a chlorine.

[32] In another embodiment, R2 is a flourine.

[33] In another embodiment, R4 is a methyl.

[34] In another embodiment, R4 is a methoxy.

[35] In another embodiment, R4 is a halogen.

[36] In another embodiment, R4 is a chlorine.

[37] In another embodiment, R4 is a flourine.

[38] In another embodiment, R4 is a cyano.

[39] In another embodiment, R7 is a C_1 alkyl.

[40] In another embodiment, R7 is a C_2 alkyl.

[41] In another embodiment, R7 is a C_2 alkyl branched with a methyl.

[42] In another embodiment, R7 is a C_3 alkyl.

[43] In another embodiment, R7 is a C_3 alkyl branched with a methyl.

[44] In another embodiment, R7 is a C4 alkyl.

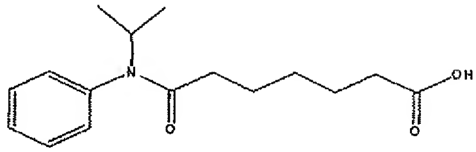
[45] In another embodiment, R7 is a C_5 alkyl.

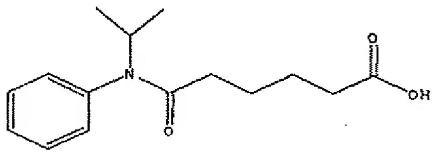
[46] In another embodiment, R7 is a C_6 alkyl.

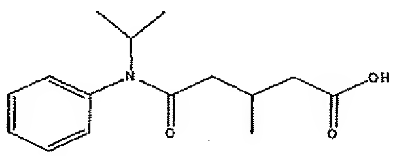
[47] In another embodiment, R7 is a C_7 alkyl.

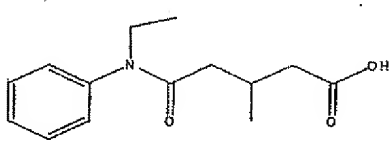
[48] In another embodiment, R7 is a C_8 alkyl.

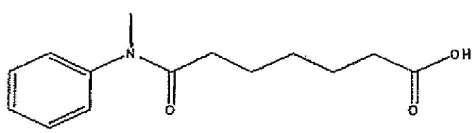
[49] Preferred compounds include, but are not limited to, the following compounds and pharmaceutically acceptable salts thereof

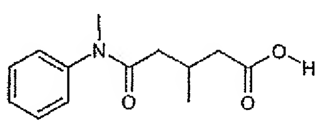
Compound 23  6-(Isopropyl-phenyl-carbamoyl)-hexanoic acid

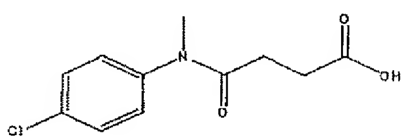
Compound 24  6-[isopropyl(phenyl)amino]-6-oxohexanoic acid

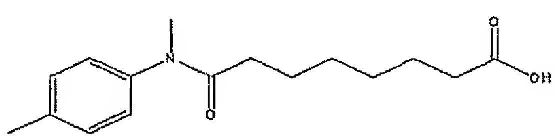
Compound 25  5-[isopropyl(phenyl)amino]-3-methyl-5-oxopentanoic acid

Compound 26  5-[ethyl(phenyl)amino]-3-methyl-5-oxopentanoic acid

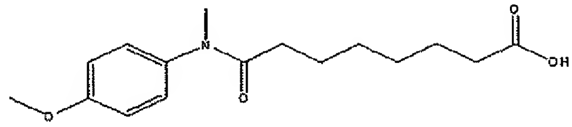
Compound 27  7-[methyl(phenyl)amino]-7-oxoheptanoic acid

Compound 28  3-methyl-5-[methyl(phenyl)amino]-5-oxopentanoic acid

Compound 29  4-[(4-chlorophenyl)(methyl)amino]-4-oxobutanoic acid

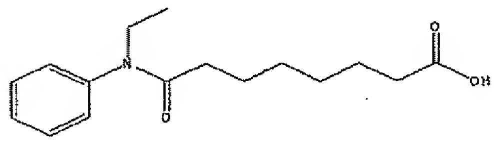
Compound 30  8-[methyl(4-methylphenyl)amino]-8-oxooctanoic acid

Compound 31



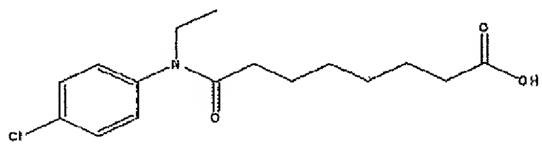
8-[(4-methoxyphenyl)(methyl)amino]-8-oxooctanoic acid

Compound 32



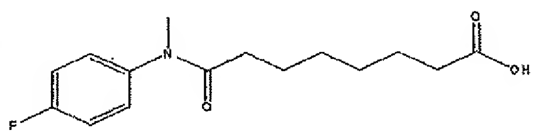
8-[ethyl(phenyl)amino]-8-oxooctanoic acid

Compound 33



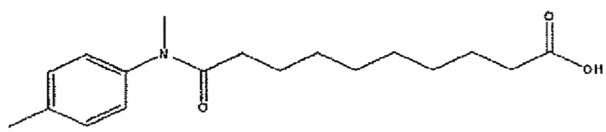
8-[(4-chlorophenyl)(ethyl)amino]-8-oxooctanoic acid

Compound 34



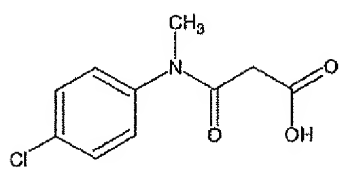
8-[(4-fluorophenyl)(methyl)amino]-8-oxooctanoic acid

Compound 35



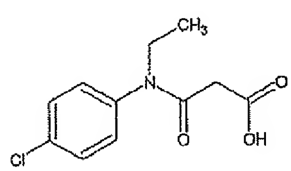
10-[methyl(4-methylphenyl)amino]-10-oxodecanoic acid

Compound 36



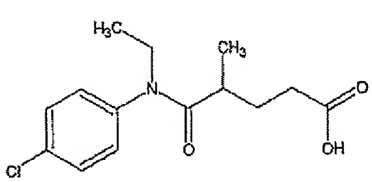
3-[(4-chlorophenyl)(methyl)amino]-3-oxopropanoic acid

Compound 37

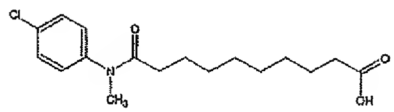
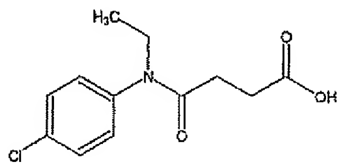
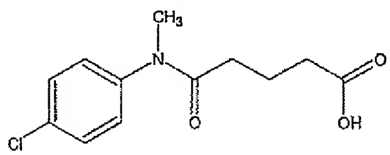
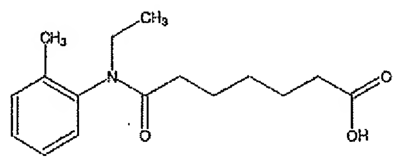
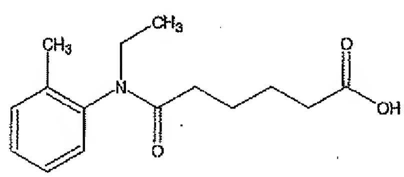
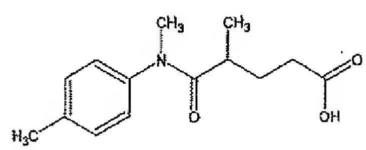
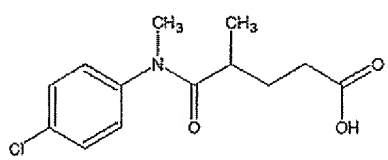
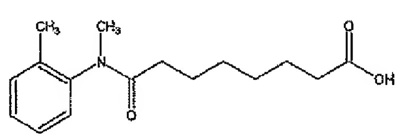


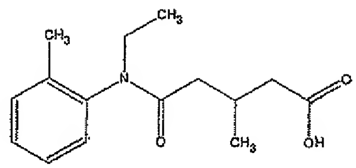
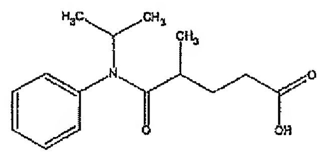
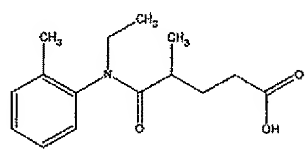
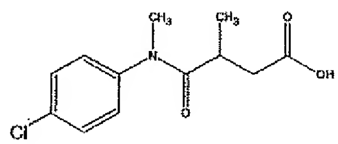
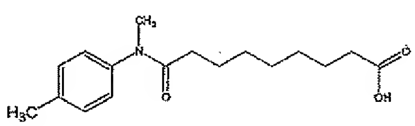
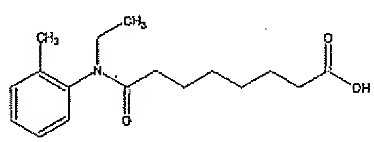
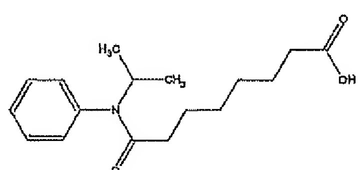
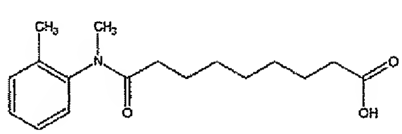
3-[(4-chlorophenyl)(ethyl)amino]-3-oxopropanoic acid

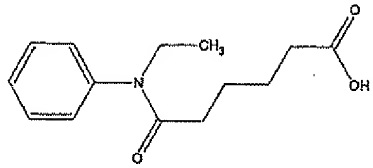
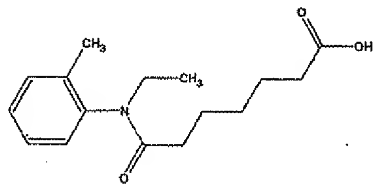
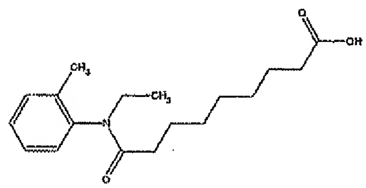
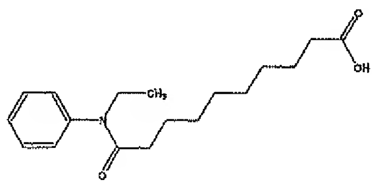
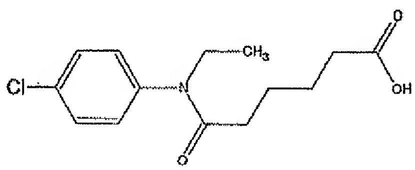
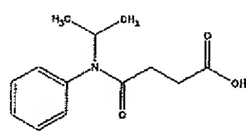
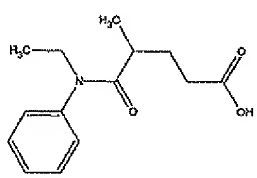
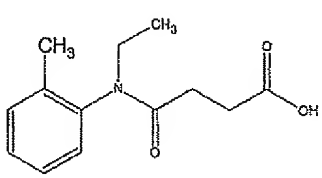
Compound 38

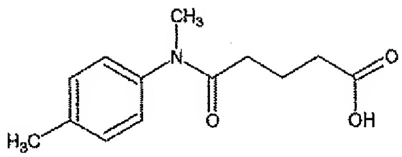
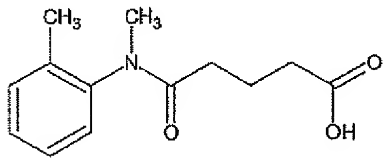
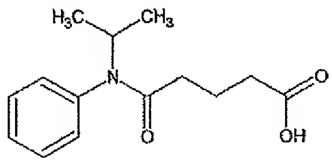
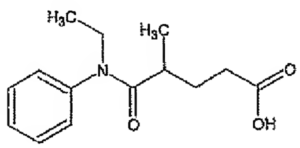
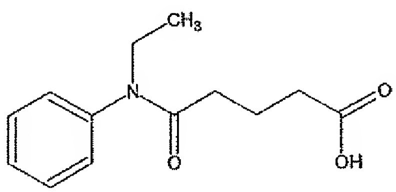
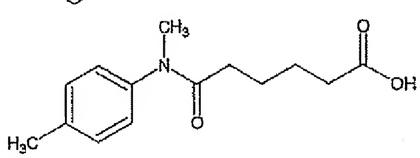
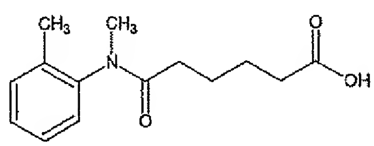
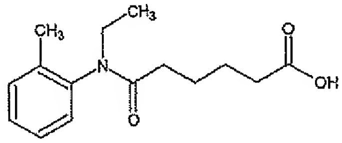


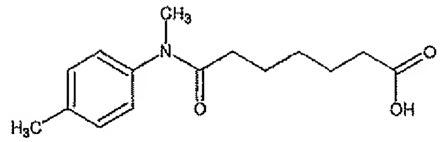
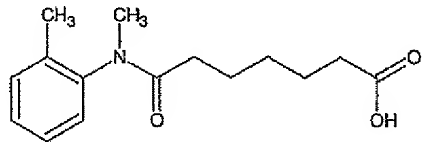
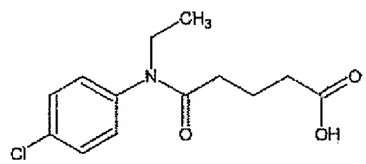
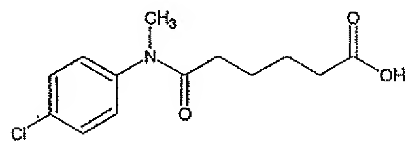
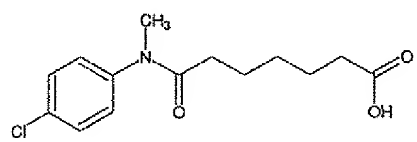
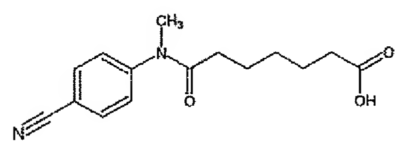
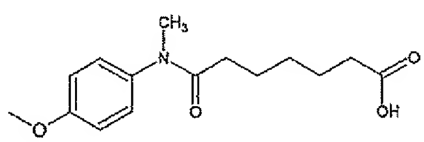
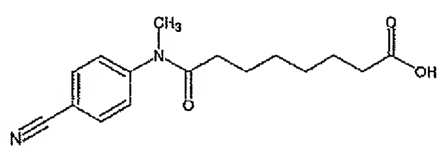
5-[(4-chlorophenyl)(ethyl)amino]-4-methyl-5-oxopentanoic acid

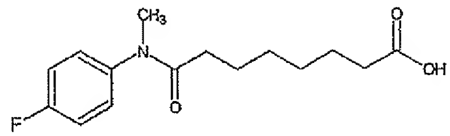
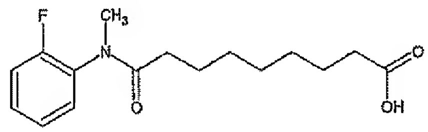
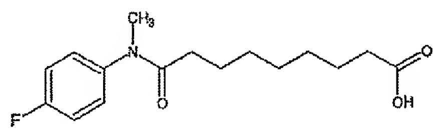
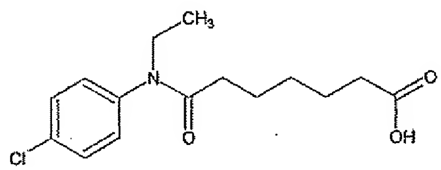
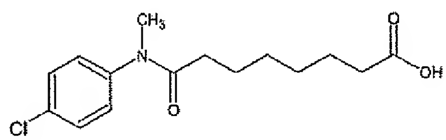
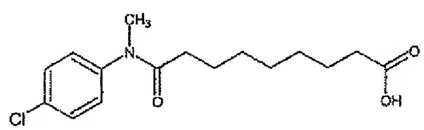
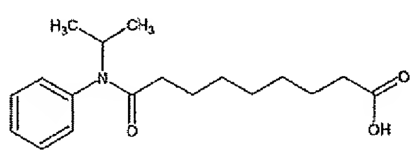
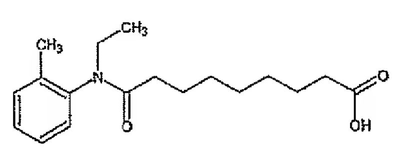
Compound 39		10-[(4-chlorophenyl)(methyl)amino]-10-oxodecanoic acid
Compound 40		4-[(4-chlorophenyl)(ethyl)amino]-4-oxobutanoic acid
Compound 41		5-[(4-chlorophenyl)(methyl)amino]-5-oxopentanoic acid
Compound 42		7-[ethyl(2-methylphenyl)amino]-7-oxoheptanoic acid
Compound 43		6-[ethyl(2-methylphenyl)amino]-6-oxohexanoic acid
Compound 44		4-methyl-5-[methyl(4-methylphenyl)amino]-5-oxopentanoic acid
Compound 45		5-[(4-chlorophenyl)(methyl)amino]-4-methyl-5-oxopentanoic acid
Compound 46		8-[methyl(2-methylphenyl)amino]-8-oxooctanoic acid

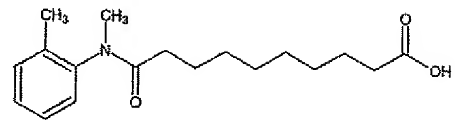
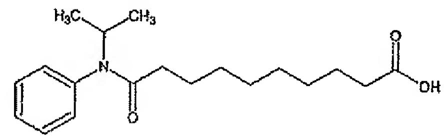
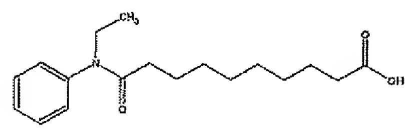
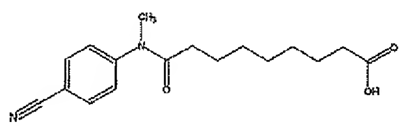
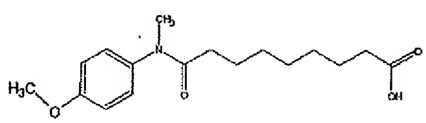
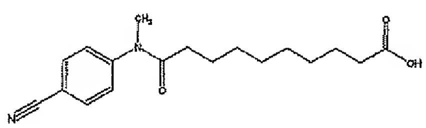
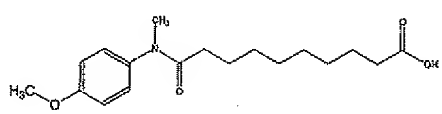
Compound 47		5-[ethyl(2-methylphenyl)amino]-3-methyl-5-oxopentanoic acid
Compound 48		5-[isopropyl(phenyl)amino]-4-methyl-5-oxopentanoic acid
Compound 49		5-[ethyl(2-methylphenyl)amino]-4-methyl-5-oxopentanoic acid
Compound 50		4-[(4-chlorophenyl)(methyl)amino]-3-methyl-4-oxobutanoic acid
Compound 51		9-[methyl(4-methylphenyl)amino]-9-oxononanoic acid
Compound 52		8-[ethyl(2-methylphenyl)amino]-8-oxooctanoic acid
Compound 53		8-[isopropyl(phenyl)amino]-8-oxooctanoic acid
Compound 54		9-[methyl(2-methylphenyl)amino]-9-oxononanoic acid

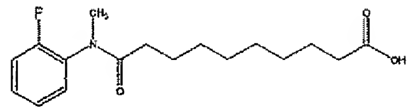
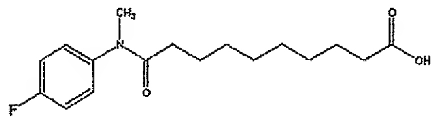
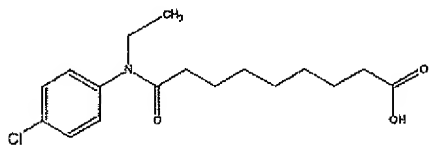
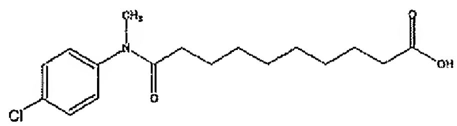
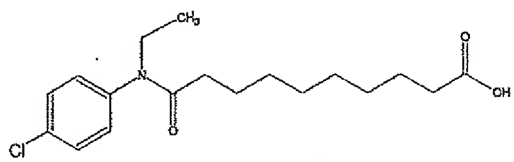
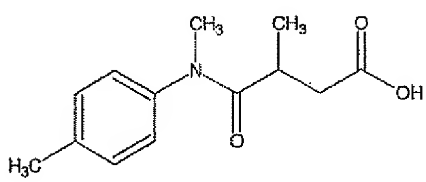
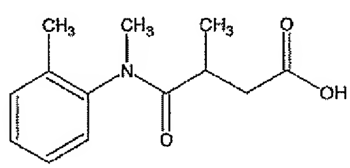
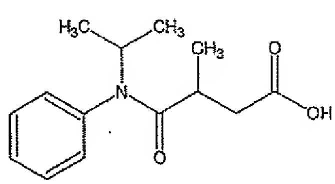
Compound 55		6-[ethyl(phenyl)amino]-6-oxohexanoic acid
Compound 56		7-[ethyl(2-methylphenyl)amino]-7-oxoheptanoic acid
Compound 57		9-[ethyl(2-methylphenyl)amino]-9-oxononanoic acid
Compound 58		10-[ethyl(phenyl)amino]-10-oxodecanoic acid
Compound 59		6-[(4-chlorophenyl)(ethyl)amino]-6-oxohexanoic acid
Compound 60		4-[isopropyl(phenyl)amino]-4-oxobutanoic acid
Compound 61		5-[ethyl(phenyl)amino]-4-methyl-5-oxopentanoic acid
Compound 62		4-[ethyl(2-methylphenyl)amino]-4-oxobutanoic acid

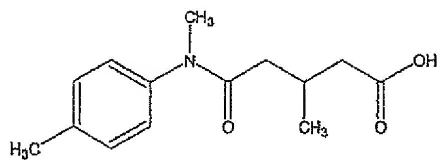
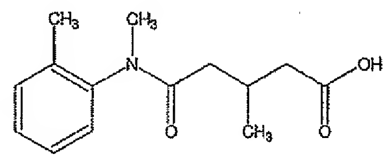
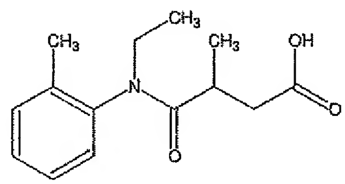
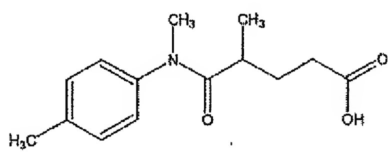
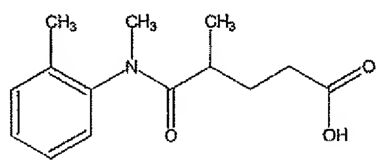
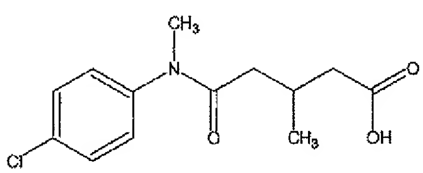
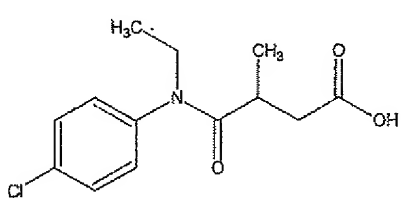
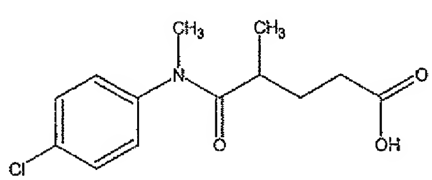
Compound 63		5-[methyl(4-methylphenyl)amino]-5-oxopentanoic acid
Compound 64		5-[methyl(2-methylphenyl)amino]-5-oxopentanoic acid
Compound 65		5-[isopropyl(phenyl)amino]-5-oxopentanoic acid
Compound 66		5-[ethyl(phenyl)amino]-4-methyl-5-oxopentanoic acid
Compound 67		5-[ethyl(phenyl)amino]-5-oxopentanoic acid
Compound 68		6-[methyl(4-methylphenyl)amino]-6-oxohexanoic acid
Compound 69		6-[methyl(2-methylphenyl)amino]-6-oxohexanoic acid
Compound 70		6-[ethyl(2-methylphenyl)amino]-6-oxohexanoic acid

Compound 71		7-[methyl(4-methylphenyl)amino]-7-oxoheptanoic acid
Compound 72		7-[methyl(2-methylphenyl)amino]-7-oxoheptanoic acid
Compound 73		5-[(4-chlorophenyl)(ethyl)amino]-5-oxopentanoic acid
Compound 74		6-[(4-chlorophenyl)(methyl)amino]-6-oxohexanoic acid
Compound 75		7-[(4-chlorophenyl)(methyl)amino]-7-oxoheptanoic acid
Compound 76		7-[(4-cyanophenyl)(methyl)amino]-7-oxoheptanoic acid
Compound 77		7-[(4-methoxyphenyl)(methyl)amino]-7-oxoheptanoic acid
Compound 78		8-[(4-cyanophenyl)(methyl)amino]-8-oxooctanoic acid

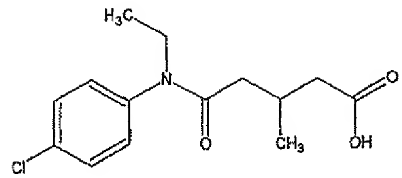
Compound 79		8-[(4-fluorophenyl)(methyl)amino]-8-oxooctanoic acid
Compound 80		9-[(2-fluorophenyl)(methyl)amino]-9-oxononanoic acid
Compound 81		9-[(4-fluorophenyl)(methyl)amino]-9-oxononanoic acid
Compound 82		7-[(4-chlorophenyl)(ethyl)amino]-7-oxoheptanoic acid
Compound 83		8-[(4-chlorophenyl)(methyl)amino]-8-oxooctanoic acid
Compound 84		9-[(4-chlorophenyl)(methyl)amino]-9-oxononanoic acid
Compound 85		9-[isopropyl(phenyl)amino]-9-oxononanoic acid
Compound 86		9-[ethyl(2-methylphenyl)amino]-9-oxononanoic acid

Compound 87		10-[methyl(2-methylphenyl)amino]-10-oxodecanoic acid
Compound 88		10-[isopropyl(phenyl)amino]-10-oxodecanoic acid
Compound 89		10-[ethyl(phenyl)amino]-10-oxodecanoic acid
Compound 90		9-[(4-cyanophenyl)(methyl)amino]-9-oxononanoic acid
Compound 91		9-[(4-methoxyphenyl)(methyl)amino]-9-oxononanoic acid
Compound 92		10-[(4-cyanophenyl)(methyl)amino]-10-oxodecanoic acid
Compound 93		10-[(4-methoxyphenyl)(methyl)amino]-10-oxodecanoic acid

Compound 94		10-[(2-fluorophenyl)(methyl)amino]-10-oxodecanoic acid
Compound 95		10-[(4-fluorophenyl)(methyl)amino]-10-oxodecanoic acid
Compound 96		9-[(4-chlorophenyl)(ethyl)amino]-9-oxononanoic acid
Compound 97		10-[(4-chlorophenyl)(methyl)amino]-10-oxodecanoic acid
Compound 98		10-[(4-chlorophenyl)(ethyl)amino]-10-oxodecanoic acid
Compound 99		3-methyl-4-[methyl(4-methylphenyl)amino]-4-oxobutanoic acid
Compound 100		3-methyl-4-[methyl(2-methylphenyl)amino]-4-oxobutanoic acid
Compound 101		4-[isopropyl(phenyl)amino]-3-methyl-4-oxobutanoic acid

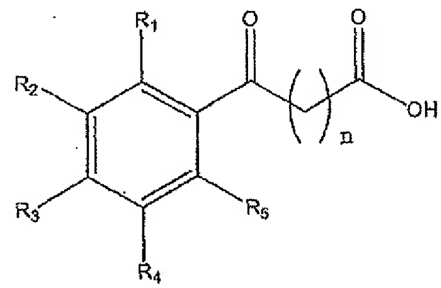
Compound 102		3-methyl-5-[methyl(4-methylphenyl)amino]-5-oxopentanoic acid
Compound 103		3-methyl-5-[methyl(2-methylphenyl)amino]-5-oxopentanoic acid
Compound 104		4-[ethyl(2-methylphenyl)amino]-3-methyl-4-oxobutanoic acid
Compound 105		4-methyl-5-[methyl(4-methylphenyl)amino]-5-oxopentanoic acid
Compound 106		4-methyl-5-[methyl(2-methylphenyl)amino]-5-oxopentanoic acid
Compound 107		5-[(4-chlorophenyl)(methyl)amino]-3-methyl-5-oxopentanoic acid
Compound 108		4-[(4-chlorophenyl)(ethyl)amino]-3-methyl-4-oxobutanoic acid
Compound 109		5-[(4-chlorophenyl)(methyl)amino]-4-methyl-5-oxopentanoic acid

Compound 110



5-[(4-chlorophenyl)(ethyl)amino]-3-methyl-5-oxopentanoic acid

[50] Other delivery agent compounds of the present invention include those of the formula:



(Compound C)

and pharmaceutically acceptable salts thereof, wherein

$n = 1$ to 9, and

R_1 to R_5 are independently hydrogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, C_2 to C_4 alkenyl, halogen, hydroxyl, $-NH-C(O)-CH_3$, or $-O-C_6H_5$.

[51] Preferred delivery agent compounds include, but are not limited to those having the following formulas and salts thereof:

[52] In one embodiment, n=2-8.

[53] In another embodiment, n=8.

[54] In another embodiment, n=7.

[55] In another embodiment, n=6.

[56] In another embodiment, n=5.

[57] In another embodiment, n=4.

[58] In another embodiment, n=3.

[59] In another embodiment, n=2 and the remaining R groups are hydrogen.

[60] In another embodiment, n=8 and the remaining R groups are hydrogen.

[61] In another embodiment, n=7 and the remaining R groups are hydrogen.

[62] In another embodiment, n=6 and the remaining R groups are hydrogen.

[63] In another embodiment, n=5 and the remaining R groups are hydrogen.

[64] In another embodiment, n=4 and the remaining R groups are hydrogen.

[65] In another embodiment, n=3 and the remaining R groups are hydrogen.

[66] In another embodiment, n=2 and the remaining R groups are hydrogen.

[67] In another embodiment, R1 and R5 are hydrogen.

[68] In another embodiment, R1 and R5 are hydrogen and n=2

[69] In another embodiment, R3 is a hydroxyl

[70] In another embodiment, R3 is a hydroxyl and N=8

[71] In another embodiment,R1 is a hydroxyl

[72] In another embodiment,R1 is a hydroxyl and N=8

[73] In another embodiment, R3 is methoxy

[74] In another embodiment, R3 is methoxy and N=2

[75] In another embodiment, R3 is methoxy and N=3

[76] In another embodiment, R2 and R4 are halogens and N=2

[77] In another embodiment R2 and R4 are flourines

[78] In another embodiment R2 and R4 are flourines and N=2

[79] In another embodiment, R1 and R3 are methyl

[80] In another embodiment, R1 and R3 are methyl and N=2

[81] In another embodiment, R2 and R4 are methyl, R3 is a methoxy and N=4

[82] In another embodiment, R3 is an isopropyl

[83] In another embodiment, R3 is an isopropyl and N=3

[84] In another embodiment, R1 is an methoxy

[85] In another embodiment, R1 is an methoxy and N=2

[86] In another embodiment, R3 is a halogen

[87] In another embodiment, R3 is a halogen and N=2

[88] In another embodiment, R3 is an fluorine and N=2

[89] In another embodiment, R3 is a methoxy

[90] In another embodiment, R3 is a methoxy and N=4

[91] In another embodiment, R2 and R4 are methyl

[92] In another embodiment, R2 and R4 are methyl and N=2

[93] In another embodiment, R2 and R4 are methyl and N=4

[94] In another embodiment, R2 and R4 are methyl and N=6

[95] In another embodiment, R2 and R3 are methyl and N=4

[96] In another embodiment, R2 and R3 are methyl and N=2

[97] In another embodiment, R1 and R4 are methyl and N=2

[98] In another embodiment, R1 and R4 are halogens

[99] In another embodiment, R1 and R4 are halogens and N=2

[100] In another embodiment, R1 and R4 are halogens and N=4

[101] In another embodiment, R1 and R4 are chlorines

[102] In another embodiment, R1 and R4 are chlorines and N=2

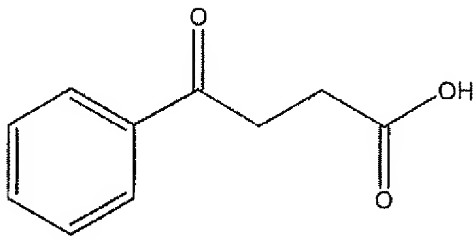
[103] In another embodiment, R1 and R4 are chlorines and N=4

[104] In another embodiment, R1 and R4 are hydroxyl

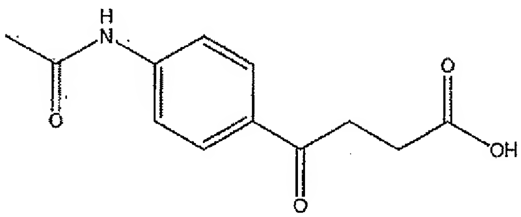
[105] In another embodiment, R1 and R4 are hydroxyl and N=8

[106] In one embodiment, compounds 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 128, 129, 130, 132, 133, 134, 136 and/or 138 or excluded from compound C.

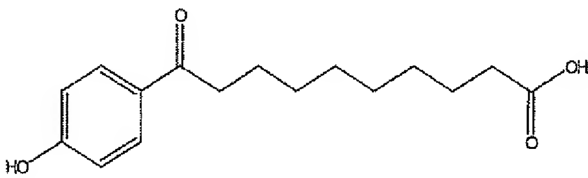
[107] Preferred compounds include, but are not limited to, those shown below.



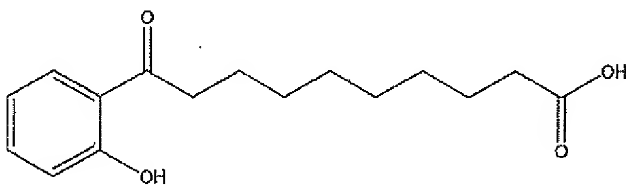
Compound 111



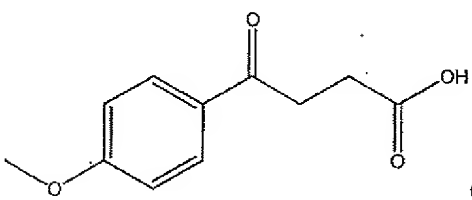
Compound 112



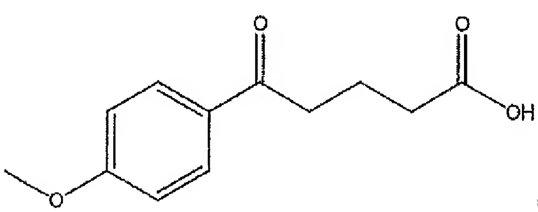
Compound 113



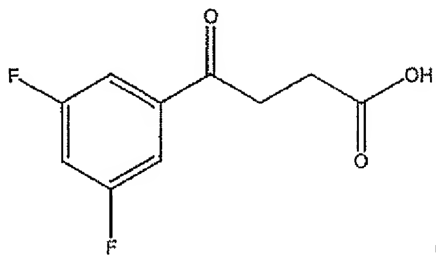
Compound 114



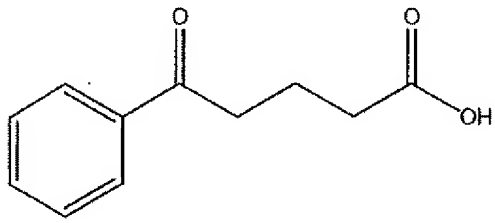
Compound 115



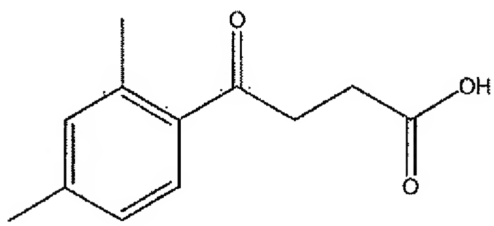
Compound 116



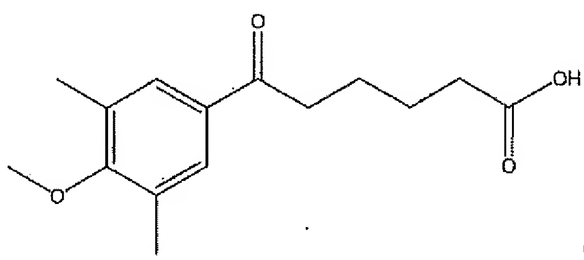
Compound 117



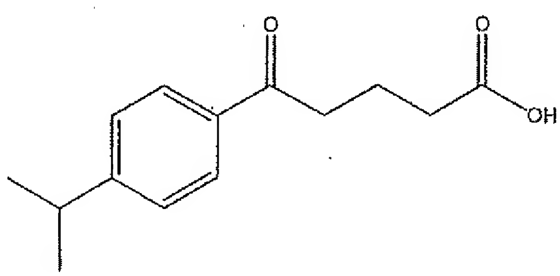
Compound 118



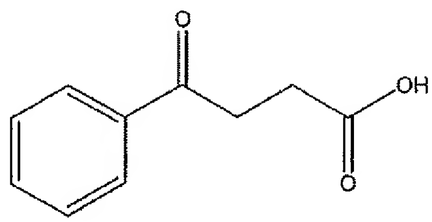
Compound 119



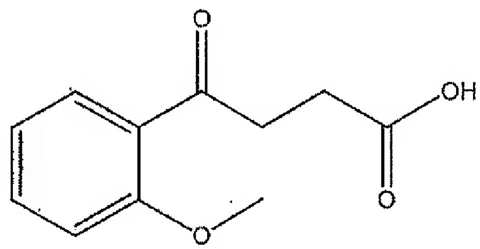
Compound 120



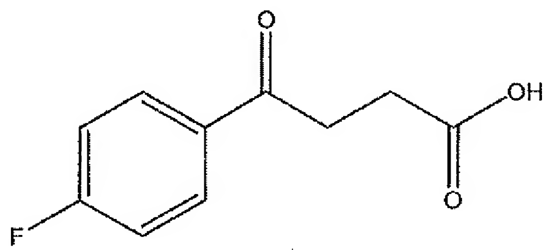
Compound 121



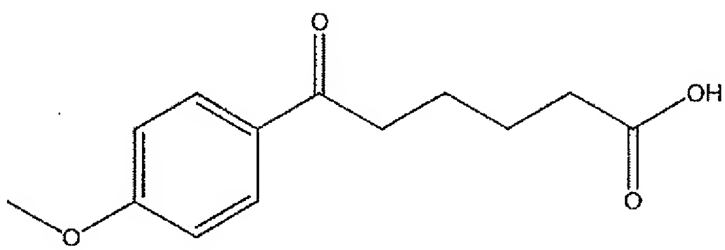
Compound 122



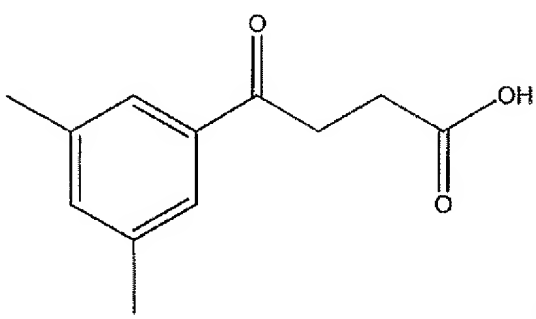
Compound 123



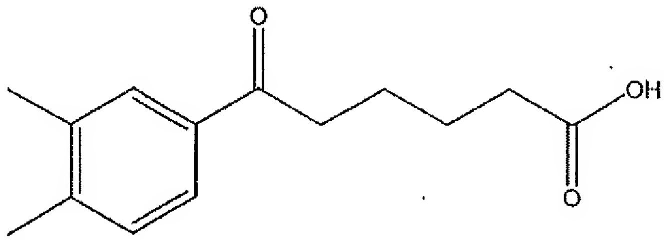
Compound 124



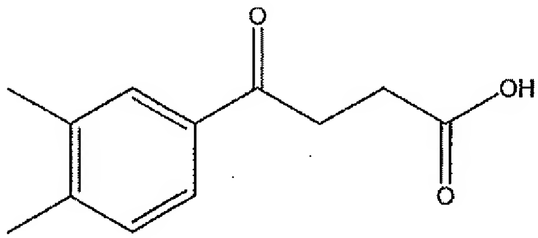
Compound 125



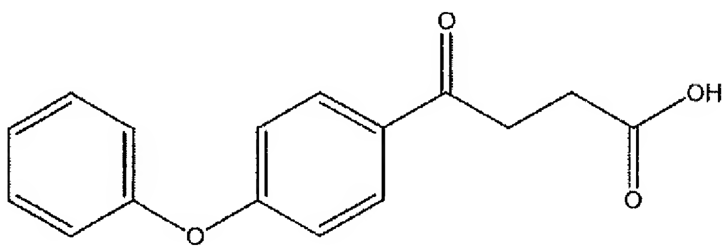
Compound 126



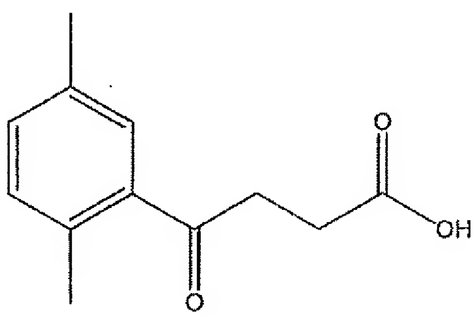
Compound 128



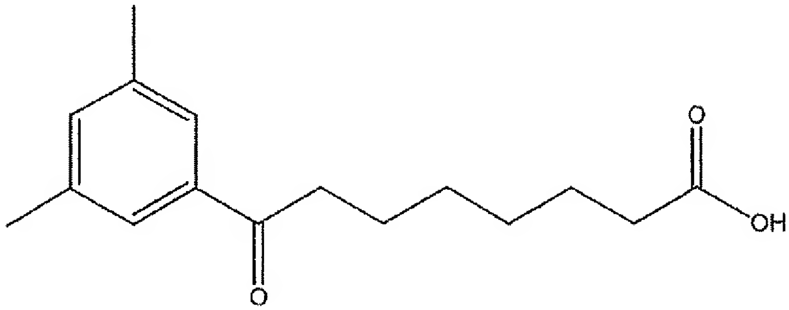
Compound 129



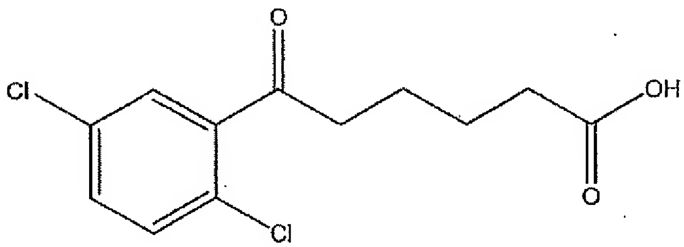
Compound 130



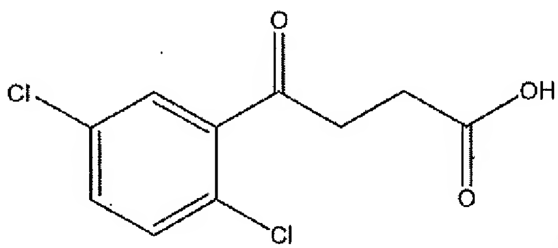
Compound 132



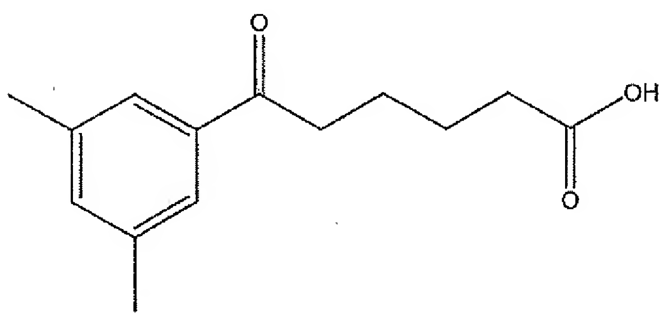
Compound 133



Compound 134

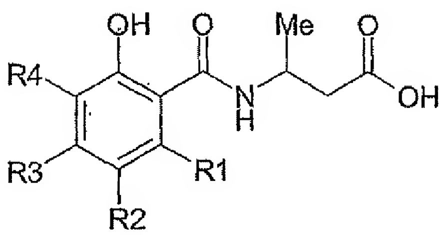


Compound 136



Compound 138

[108] Other delivery agent compounds of the present invention include those of the formula:



(Compound D)

and pharmaceutically acceptable salts thereof, wherein

R1 to R4 are independently hydrogen, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, halogen, C_1 to C_4 alkoxy, or hydroxyl.

[109] In one embodiment, R1 to R4 are independently hydrogen, methyl, methoxy, halogen, or isopropyl.

[110] In one embodiment, R1 to R4 are all hydrogen.

[111] In another embodiment R2 and R4 are halogens, preferably bromine or preferably chlorine, or preferably iodine, or preferably fluorine.

[112] In another embodiment R2 and R4 are halogens, preferably bromine or preferably chlorine, or preferably iodine, and R1 and R3 are hydrogen.

[113] In another preferred embodiment R2 and R4 are isopropyl.

[114] In another preferred embodiment R2 and R4 are isopropyl, and R1 and R3 are hydrogen.

[115] In another preferred embodiment R4 is a methyl.

[116] In another preferred embodiment R4 is a methyl and R1 to R3 are hydrogen.

[117] In another preferred embodiment R3 is a halogen, preferably chlorine.

[118] In another preferred embodiment R3 is a halogen, preferably chlorine and R1, R2 and R4 are hydrogens.

[119] In another preferred embodiment R3 is a methoxy.

[120] In another preferred embodiment R3 is a methoxy, and R1, R2 and R4 are hydrogens.

[121] In another preferred embodiment R2 is a halogen, preferably bromine.

[122] In another preferred embodiment R2 is a halogen, preferably bromine, and R1, R2 and R4 are hydrogens.

[123] In another preferred embodiment R2 is a halogen, preferably chlorine.

[124] In another preferred embodiment R2 is a halogen, preferably chlorine, and R1, R3 and R4 are hydrogens.

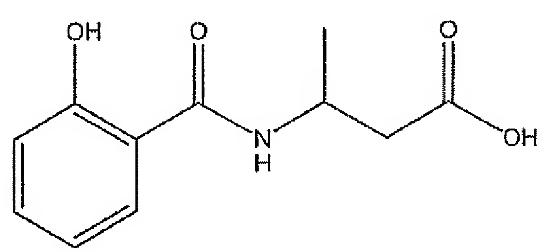
[125] In another preferred embodiment R2 is a methoxy.

[126] In another preferred embodiment R2 is a methoxy, and R1, R3 and R4 are hydrogens.

[127] In another preferred embodiment R2 is a methyl.

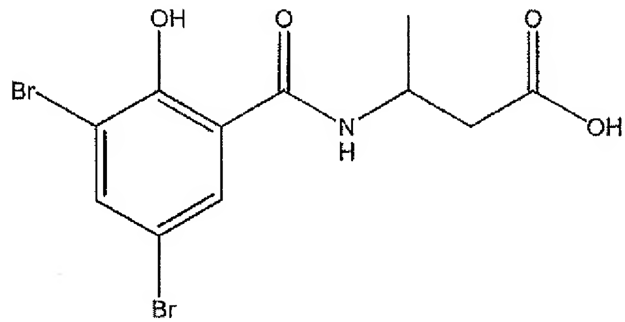
[128] In another preferred embodiment R2 is a methyl, and R1, R3 and R4 are hydrogens.

[129] Preferred delivery agent compounds include, but are not limited to those having the following formulas and salts thereof:



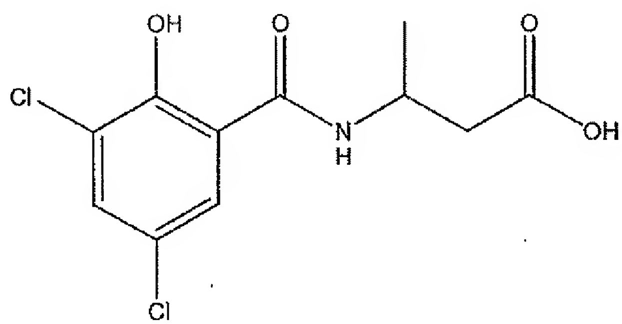
Compound 140

3-(2-Hydroxy-benzoylamino)-butyric acid



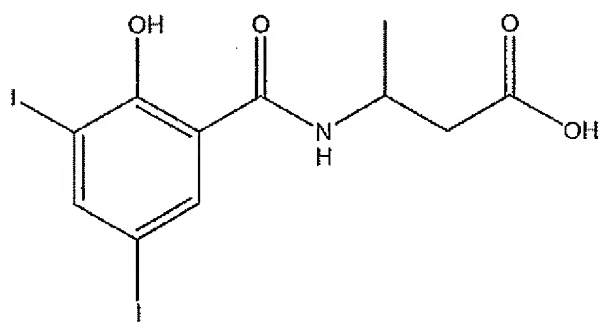
Compound 141

3-(3,5-Dibromo-2-hydroxy-benzoylamino)-butyric acid



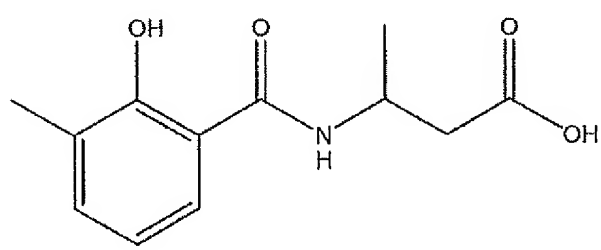
Compound 142

3-(3,5-Dichloro-2-hydroxy-benzoylamino)-butyric acid



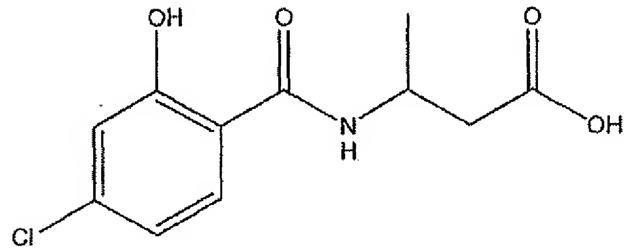
Compound 143

3-(2-Hydroxy-3,5-diiodo-benzoylamino)-butyric acid



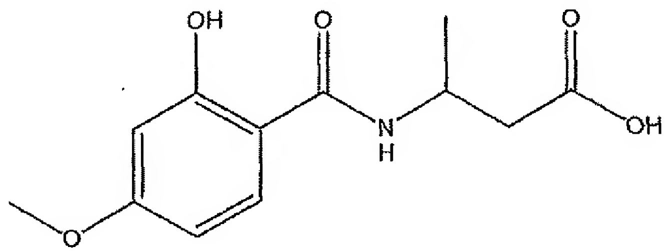
Compound 144

3-(2-Hydroxy-3-methyl-benzoylamino)-butyric acid



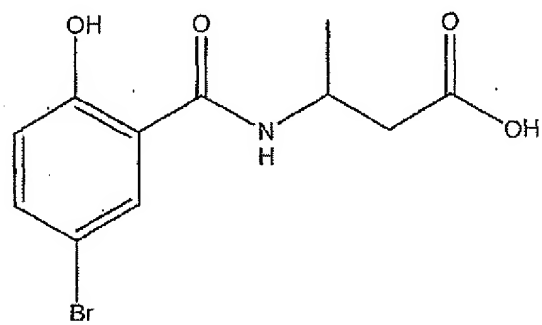
Compound 145

3-(4-Chloro-2-hydroxy-benzoylamino)-butyric acid



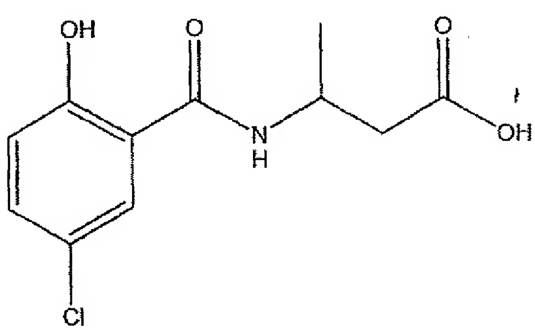
Compound 146

3-(2-Hydroxy-4-methoxy-benzoylamino)-butyric acid



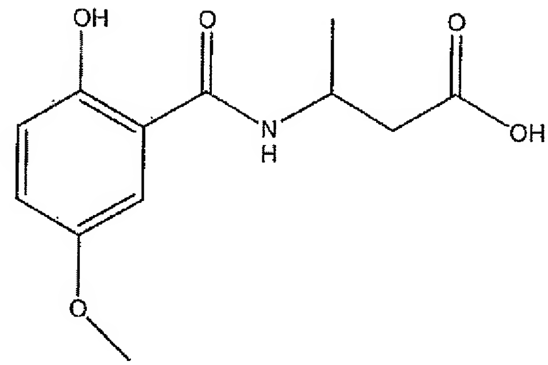
Compound 147

3-(5-Bromo-2-hydroxy-benzoylamino)-butyric acid



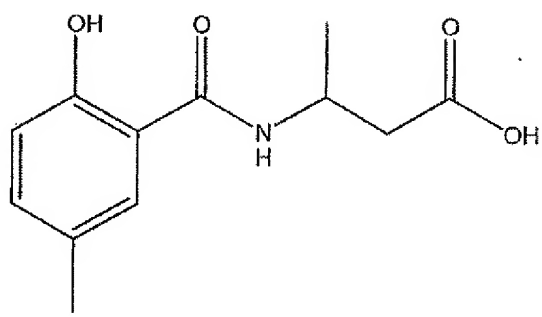
Compound 148

3-(5-Chloro-2-hydroxy-benzoylamino)-butyric acid



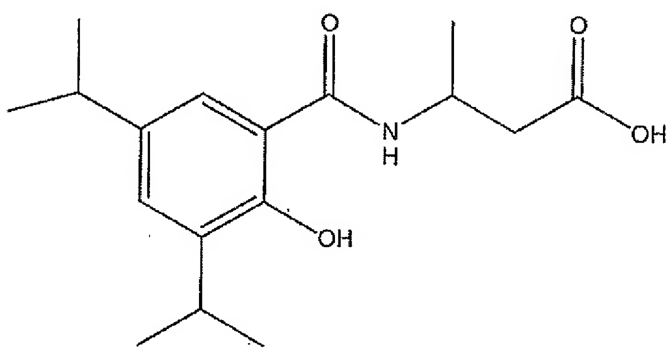
Compound 149

3-(2-Hydroxy-5-methoxy-benzoylamino)-butyric acid



Compound 150

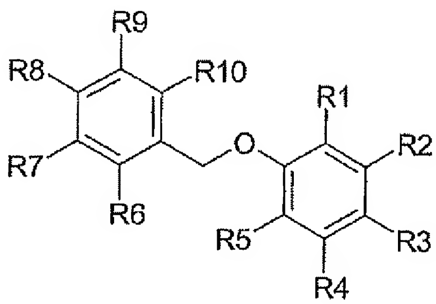
3-(2-Hydroxy-5-methyl-benzoylamino)-butyric acid



Compound 151

3-(2-hydroxy-3,5-diisopropyl-benzoylamino)-butyric acid

[130] Other delivery agent compounds of the present invention include those of the formula:



(Compound E)

and pharmaceutically acceptable salts thereof, wherein

one of R1 to R5 has the generic structure

$$-(CH_2)_n-COOH$$

where n=0 – 6;

the remaining four members of R1 to R5 are independently hydrogen, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, halogen, C_1 to C_4 alkoxy, or hydroxyl; and

R6-R10 are independently hydrogen, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, halogen, C_1 to C_4 alkoxy, or hydroxyl.

[131] In one embodiment, n=0 – 4.

[132] In another embodiment, n=0.

[133] In another embodiment, n=1.

[134] In another embodiment, R1-R10 are preferably independently hydrogen, halogen, methyl and methoxy.

[135] In another embodiment, R1-R10 are preferably independently chlorine, halogen, methyl and methoxy.

[136] In another embodiment, when the generic structure $-(CH_2)_n-COOH$ is attached at R1, rest of the R groups are hydrogen.

[137] In another embodiment, when the generic structure $-(CH_2)_n-COOH$ is attached at R1, rest of the R groups are hydrogen and n=0.

[138] In another embodiment, when the generic structure $-(CH_2)_n-COOH$ is attached at R1, rest of the R groups are hydrogen and n=1.

[139] In another embodiment, when the generic structure $-(CH_2)_n$-COOH is attached at R3, rest of the R groups are hydrogen.

[140] In another embodiment, when the generic structure $-(CH_2)_n$-COOH is attached at R3, rest of the R groups are hydrogen, and n=0.

[141] In another embodiment, when the generic structure $-(CH_2)_n$-COOH is attached at R3, rest of the R groups are hydrogen.

[142] In another embodiment, when the generic structure $-(CH_2)_n$-COOH is attached at R3, rest of the R groups are hydrogen and n=1.

[143] In another embodiment, R5 is a methoxy when the generic structure -$(CH_2)_n$-COOH is attached at R2.

[144] In another embodiment, R5 is a methoxy when the generic structure -$(CH_2)_n$-COOH is attached at R2, rest of the R groups are hydrogen.

[145] In another embodiment, R5 is a methoxy when the generic structure -$(CH_2)_n$-COOH is attached at R2, and n=0.

[146] In another embodiment, R5 is a methoxy when the generic structure -$(CH_2)_n$-COOH is attached at R2, and n=0, rest of the R groups are hydrogen.

[147] In another embodiment, R1 and R5 are methyl when the generic structure $-(CH_2)_n$-COOH is attached at R3.

[148] In another embodiment, R1 and R5 are methyl when the generic structure $-(CH_2)_n$-COOH is attached at R3, rest of the R groups are hydrogen.

[149] In another embodiment, R1 and R5 are methyl when the generic structure $-(CH_2)_n$-COOH is attached at R3 and n=0.

[150] In another embodiment, R1 and R5 are methyl when the generic structure $-(CH_2)_n$-COOH is attached at R3 and n=0, rest of the R groups are hydrogen.

[151] In another embodiment, R1 or R5 are methoxy when the generic structure $-(CH_2)_n$-COOH is attached at R3 and n=0.

[152] In another embodiment, R1 or R5 are methoxy when the generic structure $-(CH_2)_n$-COOH is attached at R3 and n=0, rest of the R groups are hydrogen.

[153] In another embodiment, R2 or R4 is a halogen, preferably chlorine when the generic structure $-(CH_2)_n$-COOH is attached at R3.

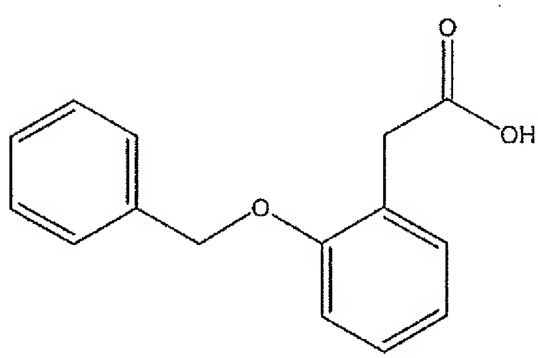
[154] In another embodiment, R2 or R4 is a halogen, preferably chlorine when the generic structure $-(CH_2)_n$-COOH is attached at R3, rest of the R groups are hydrogen.

[155] In another embodiment, R2 or R4 is a halogen, preferably chlorine when the generic structure $-(CH_2)_n$-COOH is attached at R3 and n=0.

[156] In another embodiment, R2 or R4 is a halogen, preferably chlorine when the generic structure $-(CH_2)_n$-COOH is attached at R3 and n=0, rest of the R groups are hydrogen.

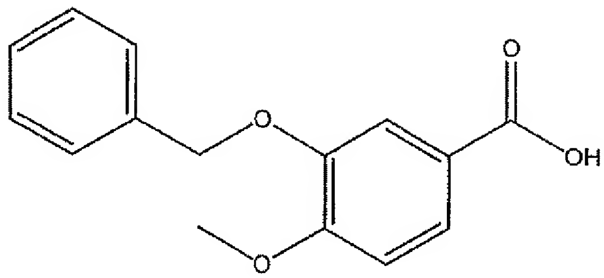
[157] In one embodiment, compounds 152, 153, 154, 155, 156, 157, and/or 158 are excluded from compound E.

[158] Preferred compounds include, but are not limited to, the following compounds and pharmaceutically acceptable salts thereof:



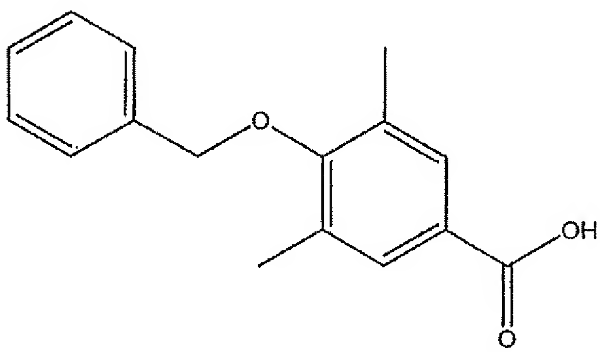
Compound 152

2-Benzyloxyphenyl acetic acid



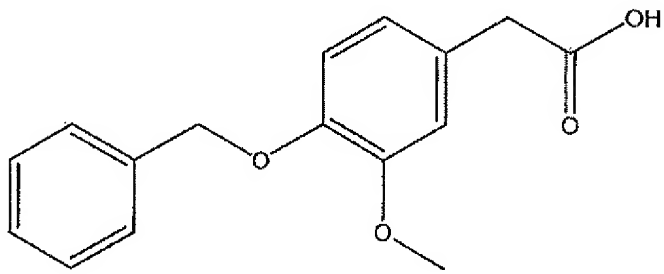
Compound 153

3-Benzyloxy-4-methoxybenzoic acid



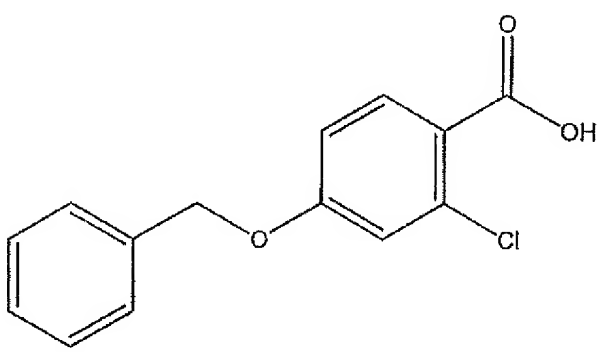
Compound 154

4-Benzyloxy-3,5-dimethylbenzoic acid



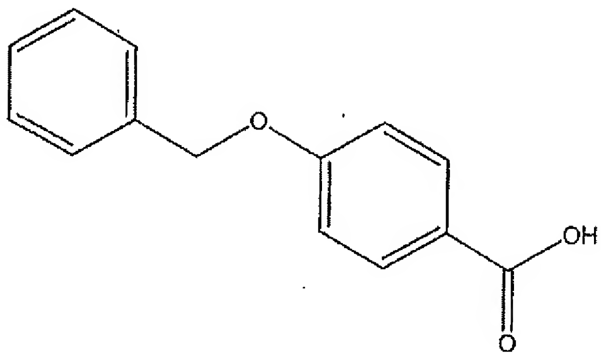
Compound 155

(4-Benzyloxy-3-methoxy-phenyl)-acetic acid



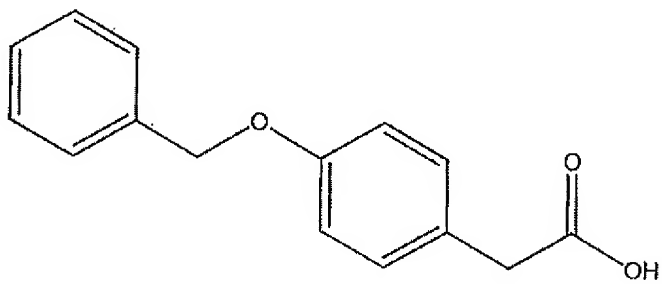
Compound 156

4-(Benzyloxy)-2-chlorobenzoic acid



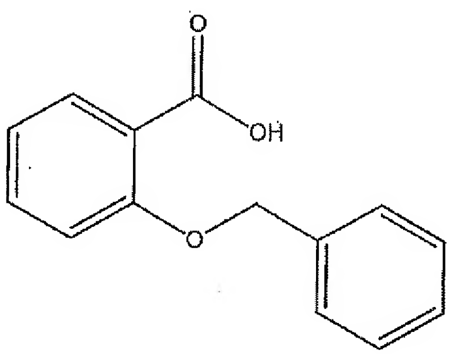
Compound 157

4-Benzyloxy-benzoic acid



Compound 158

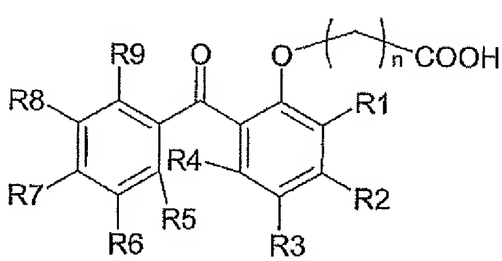
(4-Benzyloxy-phenyl)-acetic acid



Compound 159

2-Benzyloxybenzoic acid

[159] Other delivery agent compounds of the present invention include those of the formula:



Compound F

and pharmaceutically acceptable salts thereof, wherein

n = 1 to 9; and

R_1 to R_9 are independently hydrogen, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, halogen, C_1 to C_4 alkoxy, or hydroxyl.

[160] According to one preferred embodiment, n = 3 - 7, preferably, in one preferred embodiment, n=3, preferably, in another preferred embodiment, n=4; preferably, in another preferred embodiment, n=5; preferably, in another preferred embodiment, n=6; preferably, in another preferred embodiment, n=7.

[161] According to another preferred embodiment, $R_1 - R_8$ is a hydrogen.

[162] According to another preferred embodiment, R_3 is a halogen, preferably, in one embodiment, R_3 is a chlorine, preferably, in another embodiment, R_3 is a bromine.

[163] According to another preferred embodiment, R_2 is a methoxy.

[164] According to another preferred embodiment, R_2 is a methyl.

[165] According to another preferred embodiment, R_3 is a methoxy.

[166] According to another preferred embodiment, R_3 is a methyl.

[167] According to another preferred embodiment, R_6 is a methoxy.

[168] According to another preferred embodiment, R_9 is a hydrogen.

[169] According to another preferred embodiment, R_9 is a hydroxyl.

[170] According to another preferred embodiment, R_9 is a halogen, preferably, in one embodiment chlorine.

[171] According to another preferred embodiment, R_3 and R_6 are both a methoxy.

[172] According to another preferred embodiment, R_3 and R_6 are both a methoxy and the remaining R groups are hydrogen.

[173] According to another preferred embodiment, R_2 is a methyl and R_3 is a chlorine.

[174] According to another preferred embodiment, R_2 is a methyl and R_3 is a chlorine and the remaining R groups are hydrogen.

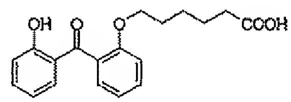
[175] According to another preferred embodiment, R_2 is a methyl and R_9 is a chlorine.

[176] According to another preferred embodiment, R_2 is a methyl and R_9 is a chlorine and the remaining R groups are hydrogen.

[177] According to another preferred embodiment, R_3 is a methyl and R_9 is a chlorine.

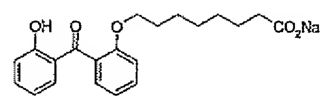
[178] According to another preferred embodiment, R_3 is a methyl and R_9 is a chlorine and the remaining R groups are hydrogen.

[179] Preferred delivery agent compounds include, but are not limited to those having the following formulas and salts thereof:



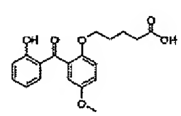
Compound 160

6-(2-(2-Hydroxybenzoyl)phenoxy)hexanoic acid



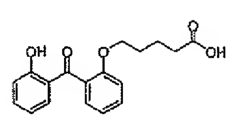
Compound 161

Sodium 8-(2-(2-Hydroxybenzoyl)phenoxy)octanoate



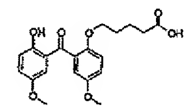
Compound 162

5-(2-(2-Hydroxybenzoyl)-4-methoxyphenoxy)valeric acid



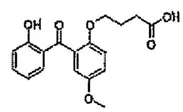
Compound 163

5-(2-(2-Hydroxybenzoyl)phenoxy)valeric acid



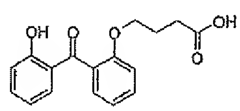
Compound 164

5-(2-(2-Hydroxy-5-methoxybenzoyl)-4-methoxyphenoxy) valeric acid



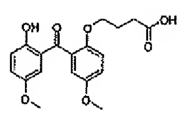
Compound 165

4-(2-(2-Hydroxybenzoyl)-5-methoxyphenoxy)butyric acid



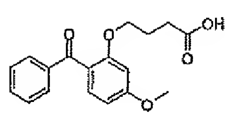
Compound 166

4-(2-(2-Hydroxybenzoyl)phenoxy)butyric



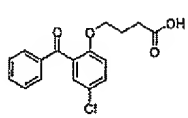
Compound 167

4-(2-Chlorobenzoyl-4-methylphenoxy)butyric acid



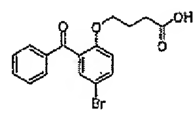
Compound 168

4-(2-Benzoyl-5-methoxyphenoxy)butyric



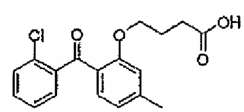
Compound 169

4-(2-Benzoyl-4-chlorophenoxy)butyric acid



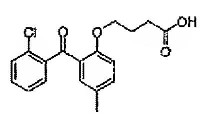
Compound 170

4-(2-Benzoyl-4-bromophenoxy)butyric acid



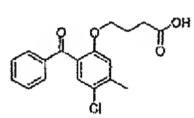
Compound 171

4-(2-(2-Chlorobenzoyl-5-methylphenoxy)butyric acid



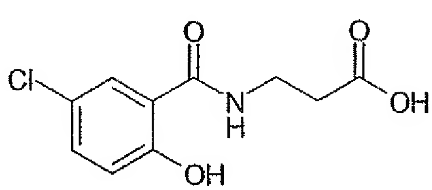
Compound 172

4-(2-(2-Chlorobenzoyl-4-methylphenoxy)butyric acid



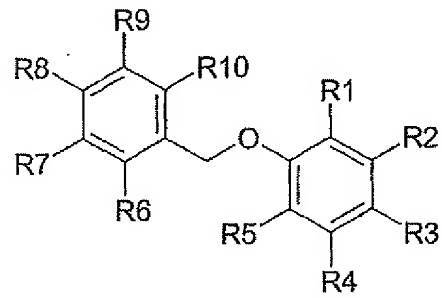
Compound 173

4-(2-Benzoyl-4-chloro-5-methylphenoxy)butyric acid



Compound 174

[180] Other delivery agent compounds of the present invention include those of the formula:



(Compound G)

and pharmaceutically acceptable salts thereof, wherein

R1-R5 are independently hydrogen, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, halogen, C_1 to C_4 alkoxy, hydroxyl, or $-O-(CH_2)_n-COOH$ (where n is 1 to 12);

at least one of R_1 to R_5 has the generic structure

$$-O-(CH_2)_n-COOH$$

where n=1 – 12; and

R6-R10 are independently hydrogen, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, halogen, C_1 to C_4 alkoxy, or hydroxyl.

[181] Preferably, only one of R1 to R5 has the formula $-O-(CH_2)_n-COOH$. In other words, four members of R1 to R5 are independently hydrogen, C_1 to C_4 alkyl, C_2 to C_4 alkenyl, halogen, C_1 to C_4 alkoxy, or hydroxyl, and the remaining member of R1 to R5 is $-O-(CH_2)_n-COOH$ (where n is 1-12).

[182] In one preferred embodiment n=1 – 12.

[183] In another preferred embodiment n= 1 – 10.

[184] In another preferred embodiment n= 1 – 6.

[185] In another preferred embodiment n= 1 – 4.

[186] In another preferred embodiment n= 10.

[187] In another preferred embodiment n= 4.

[188] In another preferred embodiment n= 1.

[189] When the generic structure -$(CH_2)_n$-COOH is attached at R1, all other R groups are hydrogen.

[190] When the generic structure -$(CH_2)_n$-COOH is attached at R1, all other R groups are hydrogen and n=3.

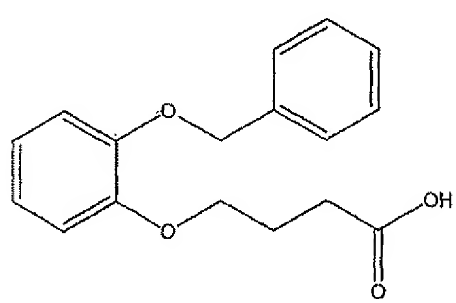
[191] When the generic structure -$(CH_2)_n$-COOH is attached at R3, all other R groups are hydrogen.

[192] When the generic structure -$(CH_2)_n$-COOH is attached at R3, all other R groups are hydrogen and n=1.

[193] When the generic structure -$(CH_2)_n$-COOH is attached at R3, all other R groups are hydrogen and n=4.

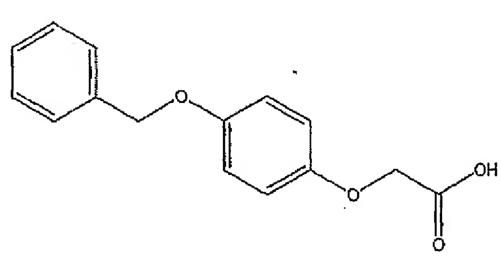
[194] When the generic structure -$(CH_2)_n$-COOH is attached at R3, all other R groups are hydrogen and n=10.

[195] Preferred compounds include, but are not limited to, the following compounds and pharmaceutically acceptable salts thereof:



Compound 175

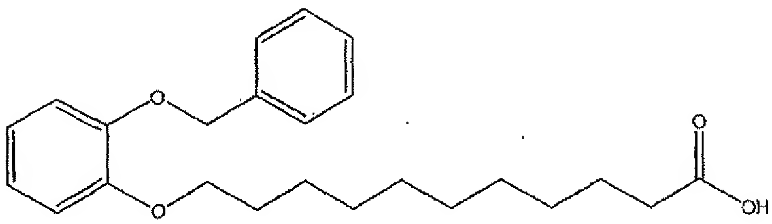
4-(2-Benzyloxy-phenoxy)-butyric acid



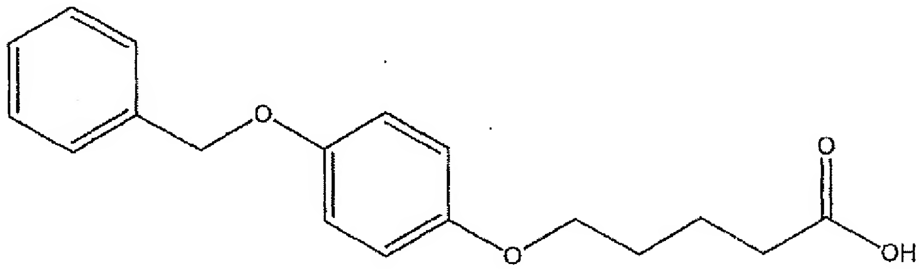
Compound 176

(4-Benzyloxy-phenoxy)-acetic acid

Compound 177



11-(2-Benzyloxyphenoxy)undecanoic acid



Compound 178

5-(4-Benzyloxy-phenoxy)-pentanoic acid

[196] Mixtures of these delivery agent compounds may also be used.

[197] The invention also provides a composition comprising the delivery agent compound of the present invention, and at least one active agent. These compositions deliver active agents to selected biological systems in increased or improved bioavailability of the active agent compared to administration of the active agent without the delivery agent compound.

[198] Also provided are dosage unit forms comprising the compositions. The dosage unit may be in the form of a liquid or a solid, such as a tablet, capsule or particle, including a powder or sachet.

[199] Another embodiment is a method for administering an active agent to an animal, by administering a composition comprising at least one of the delivery agent compounds of the present invention and the active agent to the animal. Routes of administration include the oral, intracolonic and pulmonary routes.

[200] Yet another embodiment is a method of treating a disease or for achieving a desired physiological effect in an animal by administering the composition of the present invention.

[201] Yet another embodiment is administering the composition of the present invention to an animal that would benefit from the composition and/or to an animal in need of the active agent.

[202] Yet another embodiment is a method of preparing a composition of the present invention by mixing at least one delivery agent compound of the present invention, and at least one active agent.

Detailed Description of the Invention

Definitions

[203] As used herein and in the appended claims, the singular forms "a," "an," and "the," include plural referents unless the context clearly indicates otherwise. Thus, for example, reference to "a molecule" includes one or more of such molecules, "a reagent" includes one or more of such different reagents, and reference to "the method" includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

[204] The term "polymorph" refers to a crystallographically distinct form of a substance.

[205] The term "hydrate" as used herein includes, but is not limited to, (i) a substance containing water combined in the molecular form and (ii) a crystalline substance containing one or more molecules of water of crystallization or a crystalline material containing free water.

[206] The term "solvate" as used herein includes, but is not limited to, a molecular or ionic complex of molecules or ions of a solvent with molecules or ions of delivery agent.

[207] The term "delivery agent" refers to any of the delivery agent compounds disclosed or incorporated by reference herein, including their pharmaceutically acceptable salts.

[208] An "effective amount of the pharmaceutical composition" is an amount of the pharmaceutical composition described which is effective to treat or prevent a condition in a subject to whom it is administered over some period of time, e.g., provides a therapeutic effect during a desired dosing interval.

[209] The term "treat", "treating", or "treated" refers to prophylactically preventing, curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving, or affecting a condition (e.g., a disease), the symptoms of the condition, or the predisposition toward the condition.

[210] An "effective amount of delivery agent" is an amount of the delivery agent which promotes the absorption of a desired amount of the active agent.

[211] The term "subject" includes mammals, such as rodents, cows, pigs, dogs, cats, primates, and particularly humans.

[212] The term "AUC" as used herein, means area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the complete dosing interval, e.g., 24-hour interval.

[213] The term "mean", when preceding a pharmacokinetic value (e.g., mean Peak), represents the arithmetic mean value of the pharmacokinetic value unless otherwise specified.

[214] As used herein, the term "about" means within 10% of a given value, preferably within 5%, and more preferably within 1% of a given value. Alternatively, the term "about" means that a value can fall within a scientifically acceptable error range for that

type of value, which will depend on how qualitative a measurement can be given by the available tools.

[215] "Indication" means the use for which the drug is administered either to prevent or to treat a condition, and may be used interchangeably with "treat", "treated" or "treating".

[216] The term "substituted" as used herein includes, but is not limited to, substitution with any one or any combination of the following substituents: halogens, hydroxide, C_1-C_4 alkyl, and C_1-C_4 alkoxy.

[217] The terms "alkyl", "alkoxy", "alkylene", "alkenylene", "alkyl(arylene)", and "aryl(alkylene)" include, but are not limited to, linear and branched alkyl, alkoxy, alkylene, alkenylene, alkyl(arylene), and aryl(alkylene) groups, respectively.

[218] By "peptide YY" or "PYY" is meant a Peptide YY polypeptide obtained or derived from any species. Thus, the term "PYY" includes both the human full length, 36 amino acid peptide as set forth in SEQ ID NO: 2 of International Publication No. WO 02/47712 (which is the PCT counterpart to U.S. Patent Publication No. 2002/0141985, which is hereby incorporated by reference) and Tatemoto, Proc Natl Acad Sci U.S.A. 79:2514-8, 1982, and species variations of PYY, including e.g., murine, hamster, chicken, bovine, rat, and dog PYY, for example. By "PYY agonist" is meant any compound which elicits an effect of PYY to reduce nutrient availability, for example a compound (1) having activity in the food intake, gastric emptying, pancreatic secretion, or weight loss assays described in Examples 1, 2, 5, or 6 of WO 02/47712 and U.S. Patent Publication No. 2002/0141985, and (2) which binds specifically in a Y receptor assay (Example 10 of WO 02/47712 and U.S. Patent Publication No. 2002/0141985) or in a competitive binding assay with labeled PYY or PYY [3-36] from certain tissues having an abundance of Y receptors, including e.g., area postrema (Example 9 of WO 02/47712 and U.S. Patent Publication No.

2002/0141985), wherein the PYY agonist is not pancreatic polypeptide. Preferably, PYY agonists would bind in such assays with an affinity of greater than about 1 μM, and more preferably with an affinity of greater than about 1 to about 5 nM.

[219] Such agonists can comprise a polypeptide having a functional PYY domain, an active fragment of PYY, or a chemical or small molecule. PYY agonists may be peptide or nonpeptide compounds, and include "PYY agonist analogs," which refer to any compound structurally similar to a PYY that have PYY activity typically by virtue of binding to or otherwise directly or indirectly interacting with a PYY receptor or other receptor or receptors with which PYY itself may interact to elicit a biological response. Such compounds include derivatives of PYY, fragments of PYY, extended PYY molecules having more than 36 amino acids, truncated PYY molecules having less than 36 amino acids, and substituted PYY molecules having one or more different amino acids, or any combination of the above. Such compounds may also be modified by processes such as pegylation, amidation, glycosylation, acylation, sulfation, phosphorylation, acetylation and cyclization.

[220] One such PYY agonist analog is PYY [3-36], identified as SEQ ID NO : 3 of WO 02/47712 and U.S. Patent Publication No. 2002/0141985; Eberlein, Eysselein et al., *Peptides* 10:797-803 (1989); and Grandy, Schimiczek et al., *Regul Pept* 51:151-9 (1994). Polypeptides with numbers in brackets refer to truncated polypeptides having the sequence of the full length peptide over the amino acid positions in the brackets. Thus, PYY [3-36] has a sequence identical to PYY over amino acids 3 to 36. PYY[3-36] contains approximately 40% of total peptide YY-like immunoreactivity in human and canine intestinal extracts and about 36% of total plasma peptide YY immunoreactivity in a fasting state to slightly over 50% following a meal. It is apparently a dipeptidyl peptidase-IV (DPP4) cleavage product of peptide YY. Peptide YY[3-36] is reportedly a selective ligand at the Y2 and Y5 receptors, which appear pharmacologically unique in preferring N-terminally truncated (i.e. C terminal

fragments of) neuropeptide Y analogs. A PYY agonist may bind to a PYY receptor with higher or lower affinity, demonstrate a longer or shorter half-life *in vivo* or *in vitro*, or be more or less effective than native PYY.

[221] Other suitable PYY agonists include those described in International Publication No. WO 98/20885, which is hereby incorporated by reference.

[222] The term "heparin" as used herein refers to all forms of heparin, including, but not limited to, unfractionated heparin, heparinoids, dermatans, chondroitins, low molecular weight heparin (e.g., tinzaparin (including tinzaparin sodium)), very low molecular weight heparin, and ultra low molecular weight heparin. Non-limiting examples include unfractionated heparin, such as heparin sodium (e.g., heparin sodium USP, available from Scientific Protein Labs of Waunakee, WI). Heparin generally has a molecular weight of from about 1,000 or 5,000 to about 30,000 Daltons. The term "low molecular weight heparin" generally refers to heparin in which at least about 80% (by weight) of the heparin and has a molecular weight of between about 3000 and about 9000 daltons. Non-limiting examples of low molecular weight heparin include tinzaparin, enoxaprin, and daltiparin. Tinzaparin has been approved by the U.S. Food & Drug Administration for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium. The sodium salt of from Pharmion Corporation™tinazaparin is available under the trademark Innohep of Boulder, CO. The term "very low molecular weight heparin" generally refers to heparin in which at least about 80% (by weight) of the heparin has a molecular weight of between about 1500 and about 5000 daltons. A non-limiting example of very low molecular weight heparin is bemiparin. The term "ultra low molecular weight heparin" generally refers to heparin in which at least about 80% (by weight) of the heparin has a molecular weight of between about 1000 and about

2000 daltons. A non-limiting examples of ultra low molecular weight heparin is fondiparinux.

Delivery Agents

[223] The delivery agents of the present invention may be in the free acid or a pharmaceutically acceptable salt form. Suitable pharmaceutically acceptable salts include, but are not limited to, organic and inorganic salts, for example alkali-metal salts, such as sodium, potassium and lithium; alkaline-earth metal salts, such as magnesium, calcium or barium; ammonium salts; basic amino acids, such as lysine or arginine; and organic amines, such as dimethylamine or pyridine. In one embodiment, the salts are sodium salts. The salts may be mono- or multi-valent salts, such as monosodium salts and di-sodium salts. The salts may also be solvates, including ethanol solvates, and hydrates. Non-limiting examples of pharmaceutically acceptable salts include sodium, hydrochloric acid, sulfuric acid, phosphoric acid, citric acid, acetic acid, sulfate, phosphate, chloride, bromide, iodide, acetate, propionate, hydrobromic acid, sodium hydroxide, potassium hydroxide, ammonium hydroxide, and potassium carbonate. These salts can be prepared by methods known in the art. For example, sodium salts may be prepared by dissolving the delivery agent in ethanol and adding aqueous sodium hydroxide. The delivery agent may be purified by recrystallization or by fractionation on one or more solid chromatographic supports, alone or linked in tandem. Suitable recrystallization solvent systems include, but are not limited to, acetonitrile, methanol, and tetrahydrofuran. Fractionation may be performed (i) on a suitable chromatographic support such as alumina, using methanol/n-propanol mixtures as the mobile phase, (ii) by reverse phase chromatography using trifluoroacetic acid/acetonitrile mixtures as the mobile phase, or (iii) by ion exchange chromatography using water or an appropriate

buffer as the mobile phase. When anion exchange chromatography is performed, preferably a 0-500 mM sodium chloride gradient is employed.

[224] The delivery agent may contain a polymer conjugated to it by a linkage group selected from the group consisting of -NHC(O)NH-, -C(O)NH-,-NHC(O), -OOC-, -COO-, -NHC(O)O-, -OC(O)NH-, $-CH_2NH$ $-NHCH_2-$, $-CH_2NHC(O)O-$, $-OC(O)NHCH_2-$,$-CH_2NHCOCH_2O-$, $-OCH_2C(O)NHCH_2-$, - $NHC(O)CH_2O-$, $-OCH_2C(O)NH-$, -NH-, -O-, and carbon-carbon bond, with the proviso that the polymeric delivery agent is not a polypeptide or polyamino acid. The polymer may be any polymer including, but not limited to, alternating copolymers, block copolymers and random copolymers, which are safe for use in mammals. Preferred polymers include, but are not limited to, polyethylene; polyacrylates; polymethacrylates; poly(oxyethylene); poly(propylene); polypropylene glycol; polyethylene glycol (PEG); and derivatives thereof and combinations thereof. The molecular weight of the polymer typically ranges from about 100 to about 200,000 daltons. The molecular weight of the polymer preferably ranges from about 200 to about 10,000 daltons. In one embodiment, the molecular weight of the polymer ranges from about 200 to about 600 daltons and more preferably ranges from about 300 to about 550 daltons. U.S. Patent No. 6,627,228 is hereby incorporated by reference in its entirety.

[225] The amount of delivery agent in the solid pharmaceutical composition is a delivery agent effective amount and can be determined for the particular composition by methods known to those skilled in the art. Generally, the weight ratio of delivery agent to active agent ranges from about 0.1:1 to about 1000:1 and preferably from about 1:1 to about 300:1. The weight ratio will vary according to the active agent and the particular indication for which the active agent is administered.

[226] Other suitable delivery agents for the present invention are described in U.S. Patent Nos. 6,846,844, 6,699,467, 6,693,208, 6,693,208, 6,693,073, 6,663,898,

6,663,887, 6,646,162, 6,642,411, 6,627,228, 6,623,731, 6,610,329, 6,558,706, 6,525,020, 6,461,643, 6,461,545, 6,440,929, 6,428,780, 6,413,550, 6,399,798, 6,395,774, 6,391,303, 6,384,278, 6,375,983, 6,358,504, 6,346,242, 6,344,213, 6,331,318, 6,313,088, 6,245,359, 6,242,495, 6,221,367, 6,180,140, 5,541,155, 5,693,338, 5,976,569, 5,643,957, 5,955,503, 6,100,298, 5,650,386, 5,866,536, 5,965,121, 5,989,539, 6,001,347, 6,071,510, and 5,820,881. Delivery agents of the present invention are also described in U.S. Patent Application Publication Nos. 20050009748, 20040110839, 20040106825, 20040068013, 20040062773, 20040022856, 20030235612, 20030232085, 20030225300, 20030198658, 20030133953, 20030078302, 20030072740, 20030045579, 20030012817, 20030008900, 20020155993, 20020127202, 20020120009, 20020119910, 20020102286, 20020065255, 20020052422, 20020040061, 20020028250, 20020013497, 20020001591, 20010039258, and 20010003001. Delivery agents of the present invention are also described in International Publication Nos. WO 2005/020925, WO 2004/104018, WO 2004/080401, WO 2004/062587, WO 2003/057650, WO 2003/057170, WO 2003/045331, WO 2003/045306, WO 2003/026582, WO 2002/100338, WO 2002/070438, WO 2002/069937, WO 02/20466, WO 02/19969, WO 02/16309, WO 02/15959, WO 02/02509, WO 01/92206, WO 01/70219, WO 01/51454, WO 01/44199, WO 01/34114, WO 01/32596, WO 01/32130, WO 00/07979, WO 00/59863, WO 00/50386, WO 00/47188, WO 00/40203, and WO 96/30036. Each of the above listed U.S. patents and U.S. and International published applications are herein incorporated by reference. These delivery agents may be prepared by methods known in the art, such as those described in the aforementioned patents and published patent applications. For example, SNAC may be prepared by methods known in the art, such as those described in U.S. Patent Nos. 5,650,386 and 5,866,536, and U.S. Patent Application Publication No. 2002/0065255.

Active Agents

[227] Active agents suitable for use in the present invention include biologically active agents and chemically active agents, including, but not limited to, pesticides, pharmacological agents, and therapeutic agents. Suitable active agents include those that are rendered less effective, ineffective or are destroyed in the gastro-intestinal tract including by acid hydrolysis, enzymes and the like. Also included as suitable active agents are those macromolecular agents whose physiochemical characteristics, including, size, structure or charge, prohibit or impede absorption when dosed orally.

[228] For example, an agent that is to enter the body, or that can benefit from improved pharmacokinetics including delivery, for example when oral bioavailability is limited or nonexistent. These agents are biologically or chemically active agents suitable for use in the present invention include, but are not limited to, macromolecules, such as peptides, including proteins and polypeptides, including dipeptides; hormones; and saccharides, including monosaccharides, polysaccharides, including disaccharides, mixtures of muco-polysaccharides; carbohydrates; lipids; and small polar organic molecules (*i.e.* polar organic molecules having a molecular weight of 500 daltons or less); nucleosides, other organic compounds; and particularly compounds without oral bioavailability or with limited oral bioavailability, including those compounds which by themselves do not pass (or which pass only a fraction of the administered dose) through the gastro-intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastro-intestinal tract; or any combination thereof.

[229] Further examples include, but are not limited to, the following, including synthetic, natural or recombinant sources thereof:

Amylin and Amylin Agonists;
Adrenocorticotropin;
Antigens;

Antimicrobials, including Antibiotics, Anti-Bacterials and Anti-Fungal Agents; non-limiting examples of Antibiotics include Gram-Positive Acting, Bacteriocidal, Lipopeptidal and Cyclic Peptidal Antibiotics, such as Daptomycin And Analogs thereof;
Anti-Migraine Agents such as BIBM-4096BS And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;
Antivirals including Acyclovir, Valacyclovir;
Atrial Naturetic Factor;
Bisphosphonates, including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;
Calcitonin, including Salmon, Eel, Porcine And Human;
Cholecystokinin (CCK) And CCK Agonists Including CCK-8;
Cromolyn Sodium (Sodium Or Disodium Chromoglycate);
Cyclosporine;
Desferrioxamine (DFO);
Erythropoietin;
Exedin and Exedin Agonists, including Exendin-3, Exendin-4;
Filgrastim
Follicle Stimulating Hormone (recombinant and natural);
Glucagon-Like Peptide 1 (GLP-1), Glucagon, and Glucagon-Like Peptide 2 (GLP-2);
Glucocerebrosidase;
Gonadotropin Releasing Hormone;
Growth Hormone Releasing Factor;
Growth Hormone Releasing Hormones;
Growth Hormones, Including Human Growth Hormones (hGH), Recombinant Human Growth Hormones (rhGH), Bovine Growth Hormones, And Porcine Growth Hormones;
Heparin, Including Unfractionated Heparin, Heparinoids, Dermatans, Chondroitins, Low Molecular Weight Heparin, Very Low Molecular Weight Heparin Ultra Low Molecular Weight Heparin and synthetic heparins including Fondiparinux;
Insulin, Including Porcine, Bovine, Human, And Human Recombinant, Optionally Having Counter Ions Including Zinc, Sodium, Calcium And Ammonium;
Insulin-Like Growth Factor, Including IGF-1;
Interferons, Including α (E.G., Interferon Alfacon-1 (Available As Infergen® From Intermune, Inc. Of Brisbane, Ca)), β, OMEGA and γ;
Interleukin-1; Interleukin-2; Interleukin-11; Interleukin-21;

Leutinizing Hormone and Leutinizing Hormone Releasing Hormone;
Leptin (OB Protein);
Monoclonal Antibodies including Retuxin, TNF-alpha soluble receptors;
Oxytocin;
Parathyroid Hormone (PTH), Including Its Fragments, including PTH 1-34 and PTH 1-38;
Peptide YY (PYY) Including PYY Agonists, Fragment 3-36;
Prostaglandins;
Protease Inhibitors;
Somatostatin;
Thrombopoietin;
Vancomycin;
Vasopressin;
Vitamins;
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;

[230] Including secretagogues, analogs, fragments, mimetics or polyethylene glycol (PEG)-modified derivatives of these compounds; or any combination thereof.

Delivery systems

[231] The composition of the present invention comprises one or more delivery agent compounds of the present invention, and one or more active agents. In one embodiment, one or more of the delivery agent compounds, or salts of these compounds, or poly amino acids or peptides of which these compounds or salts form one or more of the units thereof, may be used as a delivery agent by mixing with the active agent prior to administration to form an administration composition.

[232] The administration compositions may be in the form of a liquid. The solution medium may be water (for example, for salmon calcitonin, parathyroid hormone, and erythropoietin), 25% aqueous propylene glycol (for example, for heparin) and phosphate

buffer (for example, for rhGH). Other dosing vehicles include polyethylene glycol. Dosing solutions may be prepared by mixing a solution of the delivery agent compound with a solution of the active agent, just prior to administration. Alternately, a solution of the delivery agent compound (or active agent) may be mixed with the solid form of the active agent (or delivery agent compound). The delivery agent compound and the active agent may also be mixed as dry powders. The delivery agent compound and the active agent can also be admixed during the manufacturing process.

[233] The dosing solutions may optionally contain additives such as phosphate buffer salts, citric acid, glycols, or other dispersing agents. Stabilizing additives may be incorporated into the solution, preferably at a concentration ranging between about 0.1 and 20% (w/v).

[234] The administration compositions may alternately be in the form of a solid, such as a tablet, capsule or particle, such as a powder or sachet. Solid dosage forms may be prepared by mixing the solid form of the compound with the solid form of the active agent. Alternately, a solid may be obtained from a solution of compound and active agent by methods known in the art, such as freeze-drying (lyophilization), precipitation, crystallization and solid dispersion.

[235] The administration compositions of the present invention may also include one or more enzyme inhibitors. Such enzyme inhibitors include, but are not limited to, compounds such as actinonin or epiactinonin and derivatives thereof. Other enzyme inhibitors include, but are not limited to, aprotinin (Trasylol) and Bowman-Birk inhibitor.

[236] The amount of active agent used in an administration composition of the present invention is an amount effective to accomplish the purpose of the particular active agent for the target indication. The amount of active agent in the compositions typically is a pharmacologically, biologically, therapeutically, or chemically effective amount. However,

the amount can be less than that amount when the composition is used in a dosage unit form because the dosage unit form may contain a plurality of delivery agent compound/active agent compositions or may contain a divided pharmacologically, biologically, therapeutically, or chemically effective amount. The total effective amount can then be administered in cumulative units containing, in total, an effective amount of the active agent.

[237] The total amount of active agent to be used can be determined by methods known to those skilled in the art. However, because the compositions of the invention may deliver active agents more efficiently than compositions containing the active agent alone, lower amounts of biologically or chemically active agents than those used in prior dosage unit forms or delivery systems can be administered to the subject, while still achieving the same blood levels and/or therapeutic effects.

[238] The presently disclosed delivery agent compounds facilitate the delivery of biologically and chemically active agents, particularly in oral, intranasal, sublingual, gastric, intestinal, including intraduodenal, jejunal and ileul delivery, subcutaneous, buccal, intracolonic, rectal, vaginal, mucosal, pulmonary, transdermal, intradermal, parenteral, intravenous, intramuscular and ocular systems, as well as traversing the blood-brain barrier.

[239] Dosage unit forms can also include any one or combination of excipients, diluents, disintegrants, lubricants, plasticizers, colorants, flavorants, taste-masking agents, sugars, sweeteners, salts, and dosing vehicles, including, but not limited to, water, 1,2-propane diol, ethanol, olive oil, or any combination thereof.

[240] The compounds and compositions of the subject invention are useful for administering biologically or chemically active agents to any animals, including but not limited to birds such as chickens; mammals, such as rodents, cows, pigs, dogs, cats, primates, and particularly humans; and insects.

[241] The system is particularly advantageous for delivering chemically or biologically active agents that would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone (i.e. the area in which the active agent of the delivery composition is to be released) and within the body of the animal to which they are administered. Particularly, the compounds and compositions of the present invention are useful for orally administering active agents, especially those that are not ordinarily orally deliverable, or those for which improved delivery is desired.

[242] The compositions comprising the compounds and active agents have utility in the delivery of active agents to selected biological systems and in an increased or improved bioavailability of the active agent compared to administration of the active agent without the delivery agent. Delivery can be improved by delivering more active agent over a period of time, or in delivering the active agent in a particular time period (such as to effect quicker or delayed delivery), or in delivering the active agent at a specific time, or over a period of time (such as sustained delivery).

[243] Another embodiment of the present invention is a method for the treatment or prevention of a disease or for achieving a desired physiological effect, such as those listed in the table below, in an animal by administering the composition of the present invention. Preferably, an effective amount of the composition for the treatment or prevention of the desired disease or for achieving the desired physiological effect is administered. Specific indications for active agents can be found in (1) the Physicians' Desk Reference (58th Ed., 2004, Medical Economics Company, Inc., Montvale, NJ), and (2) Fauci, AS, et. al., Harrison's Principles of Internal Medicine (14th Ed., 1998, McGraw-Hill Health Professions Division, New York), both of which are herein incorporated by reference. The active agents in the table below include their analogs, fragments, mimetics, and polyethylene glycol-modified derivatives.

Active Agent	**Disease and Physiological Effect**
Amylin and Amylin Agonists;	Obesity
Adrenocorticotropin;	High Cholesterol (To Lower Cholesterol)
Antigens;	Infection
Antivirals including Acyclovir, Valacyclovir;	Viral Infections, including Herpes simplex type I and type II
Growth hormones (including human recombinant growth hormone and growth-hormone releasing factors and its analogs)	Growth disorders
Interferons, including α, β and γ	Viral infection, including chronic cancer, hepatitis, and multiple sclerosis
Interleukins (e.g. Interleukin-1; interleukin-2, interleukin-11, and interleukin-21)	Viral infection; cancer; cell mediated immunity; and transplant rejection;
Insulin; Insulin-like growth factor IGF-1	Diabetes
Heparin	Treatment and Prevention of Thrombosis, including (Deep Vein Thrombosis); prevention of blood coagulation
Calcitonin including Salmon, Eel, Porcine And Human Calcitonin;	Osteoporosis; diseases of the bone; bone pain; analgesic (including pain associated with osteoporosis or cancer)
Cholecystokinin (CCK) And CCK Agonists Including CCK-8;	Obesity
Erythropoietin	Anemia; HIV/HIV-therapy Associated Anemia; Chemotherapeutically-Induced Anemia
Atrial naturetic factor	Vasodilation
Antigens	Infection
CPHPC	Reduction of amyloid deposits and systemic amyloidoisis often (but not always) in connection with Alzheimer's disease,Type II diabetes, and other amyloid-based diseases
Monoclonal antibodies (Antibodies including Retuxin, TNF-alpha soluble receptors;)	To prevent graft rejection; cancer; used in assays to detect diseases

Active Agent	**Disease and Physiological Effect**
Leptin (OB Protein)	Obesity
Somatostatin/octreotide	Bleeding ulcer; erosive gastritis; variceal bleeding; diarrhea; acromegaly; TSH-secreting pituitary adenomas; secretory pancreatic tumors; carcinoid syndrome; reduce proptosis/ thyroid-associated ophthalmopathy; reduce macular edema/retinopathy
Protease inhibitors	HIV Infection/AIDS
Adrenocorticotropin	High cholesterol (to lower cholesterol)
Gonadotropin releasing hormone	Ovulatory disfunction (to stimulate ovulation)
Oxytocin	Labor disfunction (to stimulate contractions)
Leutinizing-hormone-releasing-hormone; follicle stimulating hormone	Regulate reproductive function
Glucocerebrosidase	Gaucher disease (to metabolize lipoprotein)
Thrombopoietin	Thrombocytopenia
Filgrastim (Granulocyte Colony Stimulating Factor); GM-CSF, (sargramostim)	shorten the duration of chemotherapy-induced neutropenia and thus treat or prevent infection in chemotherapy patients; Inhibit the growth of or to kill *Mycobacterium Intracellular Avium* Infection (MAC)
Prostaglandins	Hypertension
Cyclosporin	Transplant rejection
Vasopressin	Nocturnal Enuresis; antidiuretic
Cromolyn sodium;	Asthma; allergies
Vancomycin	Treat or prevent antimicrobial-induced infections including, but not limitted to methacillin-resistant *Staphalococcus aureus and Staph. epidermiditis*

Active Agent	Disease and Physiological Effect
gallium nitrate	Osteoporosis; Paget's disease; Inhibits osteoclasts; Promotes osteoblastic activity, hypercalcemia, including cancer related hypercalcemia, urethral (urinary tract) malignancies; anti-tumors, cancers, including urethral and bladder cancers; lymphoma; malignancies (including bladder cancer); leukemia; management of bone metastases (and associated pain); muliple myeloma, attenuate immune response, including allogenic transplant rejections; disrupt iron metabolism; promote cell migration; wound repair; to attenuate or treat infectious processes of *mycobacterium* species, including but not limited to *mycobacterium tubercolosis*, and *mycobacterium avium* complex
Desferrioxamine (DFO)	Iron overload
Parathyroid hormone (PTH), including its fragments.	Osteoporosis; Diseases of the bone
Antimicrobials	Infection including but not limited to gram-positive bacterial infection
Vitamins	Treat and prevent Vitamin deficiencies

Active Agent	**Disease and Physiological Effect**
Bisphosphonates including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;	Osteoporosis; Paget's disease; bone tumors and metastases (and associated pain); Breast cancer; including as adjuvant therapy for early stage breast cancer; management of bone metastases (and associated pain), including bone metastases associate with breast cancer, prostate cancer, and lung cancer; Inhibits osteoclasts; Promotes osteoblastic activity; treat and/or prevent bone mineral density (bmd) loss; multiple myeloma; prevention of bone complications related to malignant osteolysis; fibrous dysplasia; pediatric osteogenesis imperfecta; hypercalcemia, urethral (urinary tract) malignancies; reflex sympathetic dystropy synodrome, acute back pain after vertebral crush fracture, chronic inflammatory joint disease, renal bone disease, extrosseous calcifications, analgesic, vitamin D intoxication, periarticular ossifications
Anti-Migraine Agents such as BIBM-4096BS BIBN4096BS – (1-Piperidinecarboxamide. N-[2-[[5-amino-1-[[4-(4-pyridinyl)-1-piperazinyl)carbonyl]pentyl]amino]-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-4(1,4-dihydro-2-oxo-3(2H0-quinazolinyl)-.[R-(R*,S*)]-) And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;	Anti-migraine; calcitonin gene- related peptide antagonist
Glucagon	improving glycemic control (e.g. treating hypoglycemia and controlling hypoglycemic reactions), obesity; a diagnostic aid in the radiogical examination of the stomach, duodenum, small bowel and colon; Treat acute poisoning With Cardiovascular Agents including, but not limited to, calcium channel blockers, beta blockers
GLP-1, Exendin - 3, Exendin - 4	Diabetes; improving glycemic control (e.g. treating hypoglycemia and controlling hypoglycemic reactions), obesity
dipeptidyl peptidase IV (DPP-4) inhibitors	Diabetes; improving glycemic control (e.g. treating hypoglycemia), obesity

Active Agent	Disease and Physiological Effect
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;	Prevent or Minimize Disease or Infection
Peptide YY (PYY) and PYY-like Peptides	Obesity, Diabetes, Eating Disorders, Insulin-Resistance Syndromes

[244] For example, one embodiment of the present invention is a method for treating a patient having or susceptible to diabetes by administering insulin in a pharmaceutical formulation of the present invention. Other active agents, including those set forth in the above table, can be used in conjunction with the pharmaceutical formulations of the present invention.

[245] Following administration, the active agent present in the composition or dosage unit form is taken up into the circulation. The bioavailability of the agent can be readily assessed by measuring a known pharmacological activity in blood, e.g. an increase in blood clotting time caused by heparin, or a decrease in circulating calcium levels caused by calcitonin. Alternately, the circulating levels of the active agent itself can be measured directly.

Additives

[246] The solid pharmaceutical composition and unit dosage form of the present invention may include other active agents and pharmaceutically acceptable additives, such as excipients, carriers, diluents, stabilizers, plasticizers, binders, glidants, disintegrants, bulking agents, lubricants, plasticizers, colorants, film formers, flavoring agents, taste-masking agents, sugars, sweeteners, preservatives, dosing vehicles, surfactants, and any combination of any of the foregoing. Preferably, these additives are pharmaceutically acceptable additives, such as those described in Remington's, The Science and Practice of

Pharmacy, (Gennaro, A.R., ed., 20^{th} edition, 2003, Mack Pub. Co.), which is herein incorporated by reference.

[247] Suitable binders include, but are not limited to, starch, gelatin, sugars (such as sucrose, molasses and lactose), dibasic calcium phosphate dihydrate, natural and synthetic gums (such as acacia, sodium alginate, carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidone, polyethylene glycol, ethylcellulose, and waxes.

[248] Suitable glidants include, but are not limited to, talc and silicon dioxide (silica) (e.g, fumed silica and colloidal silicon dioxide).

[249] Suitable disintegrants include, but are not limited to, starches, sodium starch glycolate, croscarmellose sodium, crospovidone, clays, celluloses (such as purified cellullose, methylcellulose, and sodium carboxymethyl cellulose), alginates, pregelatinized corn starches, and gums (such as agar, guar, locust bean, karaya, pectin and tragacanth gums). A preferred disintegrant is sodium starch glycolate.

[250] Suitable bulking agents include, but are not limited to, starches (such as rice starch), microcrystalline cellulose, lactose (e.g., lactose monohydrate), sucrose, dextrose, mannitol, calcium sulfate, dicalcium sulfate, and tricalcium sulfate.

[251] Suitable lubricants include, but are not limited to, stearic acid, stearates (such as calcium stearate and magnesium stearate), talc, boric acid, sodium benzoate, sodium acetate, sodium fumarate, sodium chloride, polyethylene glycol, hydrogenated cottonseed, and castor oils.

[252] Suitable surfactants include, but are not limited to, sodium lauryl sulfate, hydroxylated soy lecithin, polysorbates, and block copolymers of propylene oxide and ethylene oxide.

Dosage Forms

[253] The solid pharmaceutical composition of the present invention, which includes an active agent and a delivery agent, can be formulated as a solid unit dosage form. The dosage form can be, for example, a tablet, a sachet, or a capsule, such as a hard or soft gelatin capsule. The dosage form can provide immediate, sustained, or controlled release of the delivery agent, heparin, and optionally, additional active agents.

[254] The solid pharmaceutical composition and solid unit dosage form of the present invention can be prepared as follows. A delivery agent in solid form is processed (such as by milling through a 35-mesh screen) to provide a powder having a relatively small and preferably uniform particle size. The delivery agent is then blended with a delivery agent, and optionally a filler and/or wetting agent with, for example, a V-blender or similar device, to provide a powder blend.

[255] Separately, a wetting agent mixture is prepared by mixing a wetting agent, heparin and a delivery agent. The mixture may also, for example, include water. The formulation of the wetting mixture is selected so as to wet the heparin when mixed with the aforementioned powder blend. According to one preferred embodiment, the wetting agent mixture is also formulated so as to partially solubilize the delivery agent when mixed with the powder blend.

[256] The powder blend is added to the wetting agent mixture in small increments under continuous mixing. Mixing is continued for a sufficient time (e.g., 15 minutes) after all of the powder blend has been added to obtain a uniform composition. The resulting composition is typically a semi-solid, gel, or liquid.

[257] The composition may then be formulated into a dosage form, such as a capsule, by methods known in the art. According to one preferred embodiment, the resulting composition is packed into a soft gelatin capsule or hard gelatin capsule (e.g., Size 0 Licap Capsugel Hard Gelatin capsules). Other suitable methods are described in U.S. Patent Nos.

6,605,298, 6,458,383, 6,261,601, 5,714,477, and 3,510,561; U.S. Patent Application Publication Nos. 2003/0077303 and 2001/0024658; and International Publication No. WO 88/10117, all of which are incorporated by reference.

EXAMPLES

[258] The following examples illustrate the present invention without limitation. All percentages are by weight unless otherwise specified.

[259] Proton nuclear magnetic resonance (1H NMR) analyses for the compounds listed below were conducted on a 300 MHz Bruker® spectrometer (Bruker-Physik AG, Silberstreifen, GERMANY) or a 400 MHz JEOL spectrometer (JEOL USA, Inc., Peabody, MA) using dimethyl sulfoxide (DMSO-d6) as the solvent unless otherwise indicated.

[260] Liquid chromatograph/mass spectrometry (LC-MS) analyses were performed with an Agilent Technologies (Palo Alto, California), LC/MSD 1100 (single quad) having the following parameters:

[261] Mobile Phase A: 50:950:5 acetonitrile:water:acetic acid (v/v/v).

[262] Mobile Phase B: 950:50:5 acetonitrile:water:acetic acid (v/v/v).

[263] Gradient Elution: 4 minute linear gradient 0-100% B; total time per injection is 11 minutes.

[264] Injection volume: 5uL.

[265] Column: ZORBAX Rapid Resolution Cartridge, SB-C18, 2.1 x 30 mm, 3.5 um.

[267] Particle size, catalog # 873700-902.

[268] Column temp: 40° C.

[269] UV detection at 244 nm.

[270] MSD parameters:

[271] Source: API-ES, positive polarity

[272] Scan Parameters:

Mass Range:	125.00-600.00
Fragmentor:	60 V
Gain:	1.0 EMV
Threshold:	150

Spray Chamber:

Gas Temp.	350 deg. D
Drying Gas:	12.0 l/min
Neb. Pressure;	40 psig
VCap	4000V positive/negative.

Example 1 Preparation of Compounds 1-22

[273] Compounds 1-22 were made according to the method of U.S. Patent No. 6,384,278, which is hereby incorporated by reference in its entirety.

[274] An appropriate N-substituted aniline was mixed with an appropriate dicarboxylic acid mono ester and heated in the presence of a boric acid catalyst in xylene. The intermediate carboamide was hydrolyzed to obtain the final product.

Example 2 Preparation of Compounds 23-34 and 59

[275] A dried, 200 mL, 3-necked, round-bottomed flask was equipped with a Teflon-coated magnetic bar and a vacuum jacketed Dean-Stark trap which was topped with a reflux condenser fitted with a Nitrogen inlet. The reaction vessel was charged with N-isopropyl-N-phenylamine (8.11 g, 60 mmol), boric acid (0.93g, 15 mmol,), and xylene (88 mL). To the stirred reaction mixture was added 7-ethoxy-7-oxoheptanoic acid (11.29g, 60 mmol) in one portion. The reaction was heated to reflux using a heating mantle. The

azeotroped water began to separate and was collected in the Dean-Stark trap. After 16 hours of reflux, water was collected, and the reaction was allowed to cool to ambient temperature reaction. The reaction mixture was diluted with ethyl acetate (100 mL), and was washed with an aqueous 2N solution of HCl (50 mL), and followed with a saturated solution of sodium bicarbonate (60 mL). The majority of the organic solvent was removed in vacuum. To residue was added a 2 N aqueous solution of sodium hydroxide (60 mL). The mixture was heated at 60^0C for 4 hours. Upon cooling to room temperature, the mixture was washed 60 mL of ethyl acetate. After being carefully separated from the organic layer, the aqueous phase was subjected to evaporation to remove any residual ethyl acetate. Ice was added to the aqueous solution, followed by an aqueous solution of HCl (2N, 60 mL) leading to the precipitation of a white solid. Stirring was continued for an additional 30 minutes before the precipitate was collected with a sintered funnel. The collected white solid was successfully washed with water and hexane before it was in vacuo at room temperature for 12 h to afford 7.49 g (45 %) of 7-[isopropyl(phenyl)amino]-7-oxoheptanoic acid as a white solid. HPLC: single peak at 4.83 min.; Mp: 62-63^0 C. ^{1}H NMR (DMSO-d6,) δ: 0.95-0.97 (d, 6H), 1.08-1.10 (m, 2H), 1,34-1.40 (m, 4H), 1.76-1,79 (m, 2H), 2,09-2,13 (m, 2H), 4.81-4.85 (m, 1H), 7.18-7.20 (m, 2H), 7.44-7.46 (m, 3H). Mass (M+1) : 278. Anal. Calc'd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N5.05. Found: C, 69.06; H, 8.45; N, 4.99.

[276] Compounds 24-34 and 59 were prepared from the appropriate starting materials using the same procedure.

Compound (24)

[277] HPLC: single peak at 4,43min. Mass (M+1): 264. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.95(d, 6H), 1.30(m, 2H), 1.40 (m, 2H), 1.80(m, 2H), 2.00(m, 2H), 4.80(m, 1H), 7.15(m, 2H), 7.40(m, 3H). ^{13}C NMR (100MHz , DMSO-d_6) δ: 21.0, 24.0, 24.5, 33.0, 34.0, 45.0, 128.0, 129.0, 130.0, 138.5, 170.5, 174.0.

Compound (25)

[278] HPLC: single peak at 4,62min. Mass (M+1): 264. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.78 (d, 3H), 0.94-0.95(d, 6H), 1.70-1.72(m, 1H), 1.80-1.92(m, 2H), 2.08-2.15(m, 1H), 2.20-2.30(m, 1H), 4.75-4.90(m, 1H), 7.10-7.20(m, 2H), 7.35-7.50(m, 3H). ^{13}C NMR (100MHz, DMSO-d_6) δ: 19.5, 21.0, 27.0, 40.5, 41.0, 45.0, 128.0, 129.0, 130.5, 138.5, 170.0, 174.0.

Compound (26)

[279] HPLC: single peak at 4,19min. Mass (M+1): 250. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.65 (d, 3H), 0.84-0.86(t, 3H), 1.80-1.90(m, 3H), 2.01-2.12(m, 2H), 3.49-3.53(q, 2H), 7.09-7.11(d, 2H), 7.20-7.25(m, 1H), 7.30-7.32(m, 2H). ^{13}C NMR (100MHz, DMSO-d_6) δ: 9.18, 15.87, 17.30, 23.35, 39.50, 123.98,124.72, 125.92, 138.39, 166.17, 168.27, 169.80.

Compound (27)

[280] HPLC: single peak at 3.92min. Mass (M+1): 250. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.13(m, 2H), 1.37-1.46(m, 4H), 1.99(m, 2H), 2.10-2.15(t, 2H), 3.15(s, 3H), 7.29-7.37(m, 3H), 7.42-7.47(m, 2H).

Compound (28)

[281] HPLC: single peak at 3.72 min. Mass (M+1): 236. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.79-0.81 (d, 3H), 1.93-2.02(m, 3H), 2.16-2.30(m, 2H), 3.15(s, 3H), 7.27-7.37(m, 3H), 7.43-7.48(m, 2H).

Compound (29)

HPLC: single peak at 3.88min. Mass (M+1): 242. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.21(m, 2H), 2.49(m, 2H), 3.13(s, 3H), 7.37(m, 2H), 7.58(m, 2H), 12.10 (br., 1H).

^{13}C NMR (100MHz, DMSO-d_6) δ: 28.81, 29.0, 36.5, 129.32, 129.58, 132.0, 142.66, 170.58, 173.63.

Compound (30)

[282] HPLC: single peak at 4,82 min. Mass (M+1): 278. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.02(m, 4H), 1.32(m, 4H), 1.86(m, 2H), 2.05(m, 2H), 2.21(s, 3H), 3.00(s. 3H), 7.00(m, 2H), 7.12(m, 2H), 11.85(br., 1H).

Compound (31)

[283] HPLC: single peak at 4,44 min. Mass (M+1): 294. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10(m, 4H), 1.39(m, 4H), 1.93(m, 2H), 2.11(m, 2H), 3.07(s. 3H), 3.75(s 3H), 6.96(m, 2H), 7.20(m, 2H), 11.93(br., 1H).

Compound (32)

[284] HPLC: single peak at 4.81 min. Mass (M+1): 278. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.97(t, 3H), 1.10(m, 4H), 1.39(m, 4H), 1.90(m, 2H), 2.13(m, 2H), 3.58-3.63(q, 2H), 7.09-7.24(d, 2H), 7.34(m, 1H), 7.41-7.45(m, 2H).

Compound (33)

[285] HPLC: single peak at 5.48 min. Mass (M+1): 312. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.96(t, 3H), 1.10(m, 4H), 1.40(m, 4H), 1.91(m, 2H), 2.12(m, 2H), 3.60(q, 2H), 7.27(d, 2H), 7.46(m, 2H), 11.93(br., 1H).

Compound (34)

[286] HPLC: single peak at 4,52 min. Mass (M+1): 282. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09(m, 4H), 1.39(m, 4H), 1.93(m, 2H), 2.10-2.14(m, 2H), 3.09(s. 3H), 3.75(s 3H), 7.19(m, 2H), 7.30(m, 2H), 11.91(br., 1H).

Compound (59)

[287] HPLC: single peak at 4,71min. Mass (M+1): 284. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.90(t, 3H), 1.35-1.37(m, 4H), 1.87 (t, 2H), 2.04(t, 2H), 3.52-3.57(q, 2H), 7.25(m, 2H), 7.43(m, 2H), 11.94 (s, 1H).

Example 3 Preparation of Compounds 111-139

(Compound 111) 4-Oxo-4-phenyl-butyric acid:

[289] 10g (56 mmol) of 3-benzoylpropionic acid (available from Sigma-Aldrich Co., St. Louis, MO) was added to 10 mL water. The mixture was stirred and 28 mL of 2N sodium hydroxide (aqueous) was added. The resulting solution was stirred for 2 hours and the solid product was collected after the solution was by lyophilized. 1H NMR (d6-DMSO): δ 7.9, d, 2H, (arylH's); δ 7.6, t, 1H, (arylH's); δ 7.5, t, 2H, (arylH's); δ 3.1, t, 2H (CH_2 α to carbonyl); δ 2.2, t, 2H (CH_2 α to COOH); COOH peak not observed due to water present in sample.

(Compound 113) 10-(4-Hydroxy-phenyl)-10-oxo-decanoic acid:

[290] A 500 mL flask, equipped with a reflux condenser and under inert atmosphere, was charged with decanedioic acid (20 g, 296 mmol) and acetic anhydride (280 mL, 2.96 mol). The mixture was heated to reflux for 5 hours. Acetic acid and excess acetic anhydride was removed under reduced pressure. The product was used without further purification.

[292] To a 500 mL flask, equipped with mechanical stirrer and under inert atmosphere, was added Oxacycloundecane-2,11-dione (20 g, 108.5 mmol), phenol (10.22 g, 108.5 mmol), and 200 mL carbon disulfide. Aluminum (III) trichloride (72.34 g, 542 mmol) was added and the reaction was stirred for 72 hours. Carbon disulfide was decanted away, and ice was carefully added until most of mixture was dissolved. The insoluble material was collect by suction filtration and washed with 2 X 100 mL of water. The solid was then dissolved in 100 mL of 1 M aqueous sodium hydroxide and then carefully acidified with 1 M aqueous hydrochloric acid until pH = 7.5 The solids that formed were removed by filtration and the parent solution was continued to be acidified until pH 2.5. The crude product precipitate was collected by filtration and was washed with 1 X 100 mL water. The crude product was dissolved in 100 mL of 1 M aqueous sodium hydroxide and then carefully acidified with 1 M aqueous hydrochloric acid until pH = 7.5 and the impurities that precipitated were filtered off. The parent solution was further acidified until pH 2. The crude product was collected by filtration and washed with 2X 50 mL water. The product was recrystallized form acetone. The isolated product (1.2 g, 4%) was collected by filtration. Found: C 69.00, H 7.81 %; $C_{16}H_{22}O_4$ requires C: 69.04, H: 7.97 % 1H NMR (d6-DMSO): δ 12.0, bs, 1H (COOH); δ 10.3, bs, 1H (aryl-hydroxyl); δ 7.8 d, 2H (aryl H's); δ 6.8, d, 2H, (aryl H's); δ 2.9, t, 2H (CH_2 α to carbonyl); δ 2.2, t, 2H (CH_2 α to COOH); δ 1.5, multiplet, 4H (CH_2's β to carbonyl & β to COOH), δ 1.3, multiplet, 8H (rest of CH_2's).

(Compound 114) 10-(2-Hydroxy-phenyl)-10-oxo-decanoic acid:

[293] To a 100 mL flask was added methylene chloride (50 mL), 9-bromononanol (7.63 g, 34.2 mmol) and trimethylsilyl chloride (4.5 mL, 35.5 mmol) and allowed to stir under nitrogen for 20 minutes. Triethyl amine (5.0 mL, 35.9 mmol) was then added and the resulting reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was then diluted with 80 mL of hexane, filtered, and then concentrated under reduced pressure. The resulting residue was again diluted with 80 mL of hexane, filtered, and then concentrated under reduced pressure to yield 9.7g (96%) of a yellow liquid which was used without further purification.

[294] 5.69 g (19.3 mmol) of (9-Bromo-nonyloxy)-trimethyl-silane was added drop-wise to a 50mL flask under an inert atmosphere containing magnesium metal (0.59 g, 24.3 mmol), 20 mL tetrahydrofuran and a small crystal of iodine was used to initiate the Grignard reaction. In a 100 mL flask under inert atmosphere a solution of salicylylaldehyde (2.1 mL, 19.7 mmol) in 20 mL of tetrahydrofuran was cooled with an external ice bath. The cooled aldehyde solution was then treated with 1.0 M lithium bis(trimethylsilyl)amide (20.0 mL, 20 mmol). The Grignard reaction was cooled with an external ice bath after stirring for 1 hour. The cooled Grignard was then added drop-wise via cannula to the aldehyde solution over a 5 minute period with constant stirring. The resulting reaction mixture was allowed to warm to room temperature and continue to stir overnight. The reaction was poured into 40 mL of ethyl acetate and quenched with 15 mL of saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with 2 X 25 mL portions of 4% aqueous hydrochloric acid followed by 1 X 20 mL portion of brine. The organic layer was dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. Residual salicylaldehyde was removed by Kugelrohr distillation and the resulting residue was used without further purification.

[295] A 100 mL flask was charged with 1-(2-Hydroxy-phenyl)-undecane-1,11-diol (5.0 g, 18.9 mmol) and 50 mL of dimethyl formamide. To this was added pyridinium dichromate (32.9 g, 87.5mmol). (The addition was mildly exothermic.) The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into 50 mL of ethyl acetate and washed with 200 mL of water, 30 mL of 4% aqueous hydrochloric acid, 30 mL water, and finally with 30 mL of brine. The organic layer was then stirred with 10 g of silica gel for 15 minutes, dried with sodium sulfate, filtered, and solvent removed under reduced pressure. The off-white crude product was recrystallized from

ethanol/water. The product (0.5 g, 10%) was isolated as an off-white solid, mp 85-87°C. Combustion analysis: Found: C 69.01, H 8.36 %; $C_{16}H_{22}O_4$ requires C: 69.54, H: 8.02 % 1H NMR (d6-DMSO): δ 12.0, s, 1H (COOH); δ 7.9 dd, 1H (aryl H); δ 7.5, dt, 1H, (aryl H); δ 6.9, complex multiplet, 2H (aryl H's), 3.1, t, 2H (CH_2 α to carbonyl); δ 2.2, t, 2H (CH_2 α to COOH); δ 1.6, multiplet, 2H (CH_2 β to carbonyl), δ 1.5, multiplet, 2H (CH_2 β to COOH), δ 1.3, multiplet, 8H (rest of CH_2's).

(Compound 115) 4-(4-Methoxy-phenyl)-4-oxo-butyric acid:

[296] A 500 mL round bottom flask equipped with a magnetic stirrer bar and an inert atmosphere (nitrogen gas) was charged with 5.25 mL (48.3 mmol) of anisole, 4.83 g (48.3 mmol) of succinic anhydride, 125 mL 1,1,2,2-tetrachloroethane and 125 mL of nitrobenzene. The reaction vessel was cooled with an external ice bath and stirred for 30 minutes. Aluminum trichloride (14.2 g, 106.4 mmol) was added to the pale yellow solution, which then turned to a dark reddish brown color. The ice bath was removed, and the reaction was allowed to stir at room temperature for 36 hours. Reaction was again cooled with an external ice bath. Prepared acidic solution by pouring 1N hydrogen chloride solution into a 100 mL beaker filled with ice. This solution was added to the reaction mixture carefully, drop-wise at first until reaction became clear with white precipitate. After that point a 10 mL portion was carefully added to test for reactivity, and then the remained of the ice/acid mixture was added. A second 100 mL of ice/acid mixture was added, the external ice bath removed and the pale emulsion was stirred for 2 hours. A white precipitate was collected form the emulsion by suction filtration. This solid was dissolved in 300 mL of 0.3 M sodium hydroxide, washed with 100 mL of ethyl acetate, and acidified to ~pH 1 with 1 M hydrochloric acid. The white precipitate that was collected upon vacuum filtration was washed with 3 X 100 mL de-ionized water and dried. The product (4.7 g , 47%) was isolated as a white solid, mp 149-150°C. Combustion analysis: Found: C 63.52, H 5.78%; $C_{11}H_{12}O_4$ requires C: 63.45, H: 5.81 % 1H NMR (d6-DMSO): δ 12.2, s, 1H (COOH); δ 7.9 d, 2H (aryl H's); δ 7.0, d, 2H, (arylH's); δ 3.8, s, 3H (OMe H's); δ 3.2, t, 2H (CH_2 α to carbonyl); δ 2.5, t, 2H (CH_2 α to COOH).

(Compound 116) 5-(4-Methoxy-phenyl)-5-oxo-pentanoic acid:

[297] Compound 116 was prepared similarly to compound 15, except utilizing glutaric anhydride instead of succinic anhydride, mp 141-142°C. Found : C 64.65, H 6.34%; $C_{12}H_{14}O_4$ requires C: 64.85, H: 6.35 % 1H NMR (d6-DMSO): δ 12.2, s, 1H (COOH); δ 7.9 d, 2H (aryl H's); δ 7.0, d, 2H, (arylH's); δ 3.8, s, 3H (OMe H's); δ 3.0, t, 2H (CH_2 α to carbonyl); δ 2.3, t, 2H (CH_2 α to COOH)); δ 1.8 quintuplet, 2H (CH_2 between the other two).

[298] **Compound 117** was purchased from Aldrich (St. Louis, MO), catalog number 514683.

[299] **Compound 118** was purchased from Aldrich (St. Louis, MO), catalog number B12687.

[300] **Compound 119** was purchased from Aldrich (St. Louis, MO), catalog number S346810.

[301] **Compound 120** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7013D.

[302] **Compound 121** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7148C and

(Compound 121) 5-(4-Isopropyl-phenyl)-5-oxo-pentanoic acid sodium salt:

[303] 5-(4-Isopropyl-phenyl)-5-oxo-pentanoic acid (5 g , 21.3 mmol) was dissolved in 75 mL ethanol in a 250 mL flask. Sodium hydroxide (0.85 g, 21.3 mmol) was added and the reaction was stirred overnight under reduced pressure on a rotary evaporator. The solid was dried under vacuum and used without further purification. Found: C 60.24, H 6.66, Na 9.21 %; $C_{14}H_{17}O_3Na$ requires C: 61.28, H: 6.98, Na 8.38 %

1H NMR (D2O): δ 7.7, d, 2H (aryl-H's); δ 7.2 d, 2H (aryl H's); δ 2.9, t, 2H (CH_2 α to carbonyl); δ 2.8, multiplet, 1H, (CH of isopropyl group); δ 2.1, t, 2H (CH_2 α to COOH); δ 1.8, q, 2H (CH_2 β to both carbonyl & COOH), δ 1.1, d, 6H (CH_3's of isopropyl group).

[304] **Compound 122** was purchased from Aldrich (St. Louis, MO), catalog number B13802.

[305] **Compound 123** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7060B.

[306] **Compound 124** was purchased from Fischer-Scientific (Hampton, NH), Acros, catalog number 17.522.62

[300] **Compound 125** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7011D.

[301] **Compound 126** was purchased from Reike, Aldrich (St. Louis, MO),catalog number 7036B.

[302] **Compound 128** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7012D.

[303] **Compound 129** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7012B.

[304] **Compound 130** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7055B

[305] **Compound 132** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7005b.

[306] **Compound 133** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7036F.

[307] **Compound 134** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7144D

[308] **Compound 136** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7144B.

[309] **Compound 138** was purchased from Reike, Aldrich (St. Louis, MO), catalog number 7036D.

(Compound 139)10-(2,5-Dihydroxy-phenyl)-10-oxo-decanoic acid:

[310] A 500 mL flask, equipped with a reflux condenser and under inert atmosphere, was charged with decanedioic acid (20 g, 296 mmol) and acetic anhydride (280 mL, 2.96 mol). The mixture was heated to reflux for 5 hours. Acetic acid and excess acetic anhydride was removed under reduced pressure. The product was used without further purification.

[311] To a 500 mL flask, equipped with mechanical stirrer and under inert atmosphere, was added the previously made Oxacycloundecane-2,11-dione (37.95 g, 206 mmol), 1,4-diacetoxy-benzene (20 g, 103 mmol), and 200 mL carbon disulfide. Aluminum (III) trichloride (68.7 g, 515 mmol) was added and the reaction stirred for 72 hours. Carbon disulfide was decanted away, and ice was carefully added until most of mixture was dissolved. The insoluble material was collected by suction filtration and washed with 2 X 100 mL of water. The solid was then dissolved in 50 mL of 1 M aqueous sodium hydroxide and stirred for 1 hour. The solution was acidified with 1 M aqueous hydrochloric acid until pH =2. The crude product precipitate was collected by filtration and was re dissolved in acetonitrile (50 mL) and methylene chloride (15 mL) and allowed to precipitate slowly over a week. The resulting brown powder was collected by filtration and recrystallized from 10:3 acetic acid:water. The product (0.8 g, 3%) was isolated by filtration. Found: C 65.55, H 7.69 %; $C_{16}H_{22}O_5$ requires C: 65.29, H: 7.53 % 1H NMR (d6-DMSO): δ 12.0, s, 1H (COOH); δ 11.4, s, 1H (aryl-hydroxyl); δ 9.2, s, 1H (aryl-hydroxyl); δ 7.2 d, 1H (aryl H); δ 7.0, dd, 1H, (arylH); δ 6.8, d, 1H (aryl H's), 3.0, t, 2H (CH_2 α to carbonyl); δ 2.2, t, 2H (CH_2 α to COOH); δ 1.6, multiplet, 2H (CH_2 β to carbonyl), δ 1.5, multiplet, 2H (CH_2 β to COOH), δ 1.3, multiplet, 8H (rest of CH_2's).

Example 4 – Preparation of Compounds 140-151

[312] Generally, the compounds were prepared in a four step process. First, the appropriate substituted salicylic acid and 3-amino butyric acid ethyl ester were mixed

with ethylene dichloride (EDC)/ hydroxybenzotriazole (HOBt)/Dichloromethane (DCM). Second, the basic ion exchange resin A-15/A-21 (available from Rohm and Haas, Philadelphia, PA) was added. Third, after partial workup, the product was reacted with potassium trimethylsilanolate (KOTMS)/tetrahydrofuran (THF). Forth, IRC-50 resin (Rhohm & Haas, Philadelphia, PA) was added.

[313] To each scintillation vial was added a salicylic acid (4.57mmol), DCM (10 mL), EDC (1.05 g, 5.48 mmol), HOBt (838 mgs, 5.48 mmol), DMF (2 mL), and ethyl-3-aminobutyrate (600 mgs, 4.57 mmol). All vials were capped tightly, placed on a J-Kem reaction block (J-Kem Scientific Inc., St. Lois, MO), and shaken and heated (150 rpm, 35 °C) overnight. Based on TLC, all reactions have one predominant spot. To each vial was added Amberlyst-21 and Amberlyst-15 resins (approximately 2.5 g, 11 mmol) and shaking at ambient temperature was continued overnight. The reactions were filtered, the resins washed with DCM (2 x 5 mL), and the combined filtrates of each reaction collected in a fresh scintillation vial. The filtrates were blown down under a stream of nitrogen to a volume of about 2 mL.

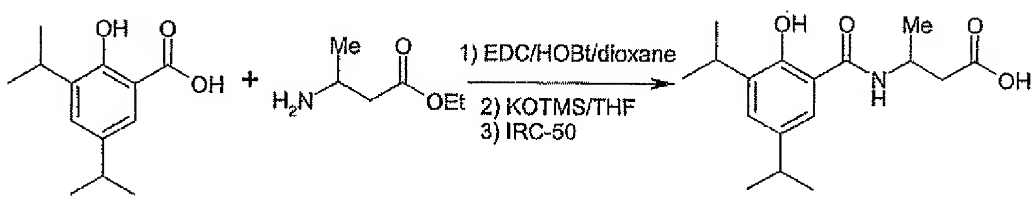
[314] To each vial was added a 1.2 M solution of potassium trimethylsilanolate (KOTMS) in THF (10 mL, 12 mmol). More THF was added to some reactions as necessary to obtain shakable slurries. All vials were capped tightly, placed on a J-Kem reaction block, and shaken and heated (150 rpm, 60 °C, 6 h). The reaction block was cooled, and IRC-50 resin (3 g, 30 mmol) was added to each vial to quench the potassium salt. DCM was added as necessary to suspend the resin and facilitate shaking. The reactions were shaken overnight. The reactions were filtered, the resins washed with DCM (2 x 5 mL), when necessary washed with DMF to dissolve solids, and the combined filtrates of each reaction collected in a fresh, tared scintillation vial. At this point small aliquots of the filtrates were taken and diluted with 1:1 ACN/H_2O for LC-MS. The filtrates were blown down under a stream of nitrogen. To remove traces of DMF, the vials were placed in a 50 °C vacuum oven.

[315] Based on LC-MS analysis, some reaction mixtures still contained considerable amounts of ester. These library members were retreated with KOTMS. To each vial was added a 1.2 M solution of KOTMS in THF (8 mL, 9.6 mmol). All vials were capped tightly, put in a Pierce reaction block , stirred and heated (60 °C, 5 h). The reaction block was

cooled, and IRC-50 resin (2 g, 20 mmol) was added to each vial to quench the potassium salt. DCM was added as necessary to suspend the resin and facilitate stirring. The reactions were stirred over the weekend. The reactions were filtered through a plug of silica, the resins and silica washed with DCM (1 x 5 mL), then 2:5 MeOH/DCM (3 x 7mL) and the combined filtrates of each reaction collected in a fresh, tared scintillation vial. At this point small aliquots of the filtrates were taken and diluted with 1:1 ACN/H_2O for LC-MS. The filtrates were blown down under a stream of nitrogen.

[316] All other reaction mixtures from the first KOTMS treatment were taken up in 10:1 DCM/MeOH and filtered through a plug of silica, eluting with more 10:1 DCM/MeOH. At this point small aliquots of the filtrates were taken and diluted with 1:1 ACN/H_2O for LC-MS. The filtrates were blown down under a stream of nitrogen.

Alternative Preparation of Compound 140-151:



[317] To a 1 L round-bottomed flask was added 3,5-diisopropylsalicylic acid (25.0 g, 112.5 mmol), HOBt (20.6 g, 135.0 mmol), ethyl-3-aminobutyrate (18.0 g, 123.7 mmol) and dioxane (400 mL). The resulting mixture was stirred at ambient temperature. EDC (25.9 g, 135.0 mmol) was added in portions and stirring continued overnight. An HPLC of the reaction mixture at this point showed HOBt, perhaps a trace of starting salicylic acid, and one new predominant product. Another portion of EDC (5 g, 26.0mmol) was added and stirring continued overnight. Another HPLC showed essentially no change. The reaction was quenched with water (400 mL) and the dioxane stripped off by rotary evaporator. The resulting oil/water mixture was poured into a 1L separatory funnel and DCM (400 mL) was added. Lots of white solid formed. EtOAc was added in an attempt to get separation of layers, with no success. The separatory funnel was drained and the mixture stripped of organics on

the rotary evaporator. The water/oil mixture was extracted with EtOAc (500 mL, then 200 mL). The combined EtOAc layers were washed with aqueous HCl (10%, 2 x 200 mL), aqueous NaOH (10%, 2 x 200 mL) and brine (50 mL, then 200 mL). The organics were dried over Na_2SO_4 and stripped down on the rotary evaporator to a brown oil that contained small amounts of white solid. HPLC analysis indicates the white solid is residual HOBt, and the brown oil is desired product. The brown oil was pipetted out of the flask, avoiding as much of the white solid as possible. The brown oil was taken up in EtOAc (500 mL), washed with NaOH (10%, 2 x 200 mL) and dried over Na_2SO_4. The EtOAc was stripped off on the rotary evaporator to obtain the brown oil. HPLC at this point indicates one predominant peak and no HOBt.

[318] The viscous oil was dissolved in THF (200 mL) and KOTMS (31.7 g, 247.4 mmol) was added. The resulting viscous mixture was stirred overnight. HPLC indicated reaction completion to one peak. Added IRC-50 resin (37 g, 370 mmol, 1.5 eq.) and 100 mL DCM to suspend the resin, then stirred several hours. Filtered, washed the resin with DCM (3 x 50 mL) and concentrated on the rotary evaporator to a brown oil. An attempt to recrystallize from ACN/acetone was unsuccessful. It was determined based on solubility at this point that the material was predominantly the potassium salt. The oil was taken up in H_2O/ACN, heated until clear, filtered while hot, and cooled to ambient temperature. The filtrate was treated with aqueous HCl and the resulting solid precipitate was isolated and ground into a powder to obtain E1528: 9.13 grams, HPLC rt 6.7 min 100%, KF 0.47, NMR consistent with structure, Elemental analysis theoretical C:66.11, H:8.21, N:4.54, found C:65.62, H:8.19, N:4.46.

Compound Number and Name	MW	MS (M+H)	Approximate percent purity based on LC-MS
Compound 140 3-(2-Hydroxy-benzoylamino)-butyric acid	223.2306	224	83

Compound 141 3-(3,5-Dibromo-2-hydroxy-benzoylamino)-butyric acid	381.0326	382	71
Compound 142 3-(3,5-Dichloro-2-hydroxy-benzoylamino)-butyric acid	292.1206	292	77
Compound 143 3-(2-Hydroxy-3,5-diiodo-benzoylamino)-butyric acid	475.0234	476	82
Compound 144 3-(2-Hydroxy-3-methyl-benzoylamino)-butyric acid	237.2577	238	75
Compound 145 3-(4-Chloro-2-hydroxy-benzoylamino)-butyric acid	257.6756	258	82
Compound 146 3-(2-Hydroxy-4-methoxy-benzoylamino)-butyric acid	253.2571	254	75
Compound 147 3-(5-Bromo-2-hydroxy-benzoylamino)-butyric acid	302.1316	303	82

Compound 148 3-(5-Chloro-2-hydroxy-benzoylamino)-butyric acid	257.6756	258	78
Compound 149 3-(2-Hydroxy-5-methoxy-benzoylamino)-butyric acid	253.2571	254	77
Compound 150 3-(2-Hydroxy-5-methyl-benzoylamino)-butyric acid	237.2577	238	82
Compound 151 3-(2-hydroxy-3,5-diisopropyl-benzoylamino)-butyric acid	307.3931	308	89

Example 5 – Obtaining Compounds 152-160

[319] **Compound 152** - was purchased from Transworld Chemical (South Melborne, AUSTRALIA).

[320] **Compound 153** - was purchased from Lancaster (Windham, NH).

[321] **Compound 154** - was purchased from Avocado (Heysham, Lancashire, ENGLAND).

[322] **Compound 155** - was purchased from Aldrich under catalog number 42919 (St. Louis, MO).

[323] **Compound 156** - was purchased from Sigma-Aldrich (St. Louis, MO).

[324] **Compound 157** - was purchased from Sigma (St. Louis, MO).

[325] **Compound 158** - was purchased from Matrix Scientific (Columbia, SC).

Compound	HPLC Retention Time	HPLC Protocol	KF Value	Melting Point Range Value	CHNC C	CHNC H	CHNF C	CHNF H
152	5.41		0					
153	5.1 min	0.1% TFA	0		69.76	5.46		
154	6.2 min	0.1% TFA	0		74.98	6.29		
155	5.21		0					
156	5.82 min	0.1% TFA	0					
157	5.42		0	184-186	73.67	5.3	72.56	4.91
158	5.47		0	110-112	74.36	5.82	74.39	5.66
159	5.56 min				63.47	5.39	62.65	5.13
160	5.30		0.3	67-70	73.45	5.32	73.08	5.37

Compound 160:

[326] Potassium hydroxide (10.37 g, 184.8 mmol) was ground to a powder with a mortar and pestle and added to a 250 mL flask containing 75 mL of dimethyl sulfoxide and 2-hydroxy-benzoic acid methyl ester (7.03 g, 46.2 mmol). To this mixture was added benzyl bromide (7.91 g, 46.2 mmol) and allowed to mix for 4 hours with stirring. Water (100 mL) was added and the reaction stirred for an additional 30 minutes. The reaction was then cooled with an external ice bath to 0°C and acidified with concentrated hydrochloric acid to a pH 1. The mixture was extracted with 3 x 230 mL ethyl acetate. The organic layers were combined and solvent removed under reduced pressure. The resulting yellow liquid was dissolved in ethyl acetate (50 mL) and washed with 2 X 30 mL water followed by 2 X 30 mL brine. The organic layer was dried over sodium sulfate, filtered, and solvent removed under reduced pressure. The resulting yellow liquid was dried under vacuum for several days, and white crystalline solid formed. The solid product was collected and dried further under vacuum. Product (8.04 g, 76%) was isolated as a white crystalline solid, mp 67-70°C. Combustion analysis: Found: C 73.08, H 5.37%; $C_{14}H_{12}O_3$ requires C 73.45, H 5.32 %;

Example 6 – Preparation of Compounds 160-167

[326] Compound F was prepared according to the general scheme, wherein a 2-hydroxybenzophenone was alkylated with a bromoalkyl ester in the presence of a base, followed by cleavage of the ester moiety using potassium trimethylsilanoate

[327] **(Compound 160) 6-(2-(2-Hydroxybenzoyl)phenoxy)hexanoic acid:** A 250 mL round bottom flask equipped with a magnetic stirrer bar and a reflux condenser was charged with 10.32 g (48.2 mmol) of 2,2'-dihydroxybenzophenone and 100 mL of dimethylsulfoxide (DMSO). Potassium hydroxide (2.91 g, 51.9 mmol) that had been ground to a powder was added to the clear solution. The reaction mixture was heated to 45°C, until most of the solid had dissolved. The resulting red slurry was treated with 8.80 mL (11.04 g, 49.5 mmol) of ethyl 6-bromohexanoate. After stirring for 20 hr at 25°C, the clear reaction mixture was diluted with aqueous 1 % hydrochloric acid and methyl t-butyl ether (MTBE). The layers were separated. The organic phase was washed with water (2 X 50 mL) and brine (1 X 40 ML), dried over sodium sulfate and concentrated. The residue was taken up in 100 mL of tetrahydrofuran (THF) and treated with potassium trimethylsilanoate (15.09 g, 118 mmol). The orange solution was stirred for 20 hr at 25°C, diluted with aqueous 4% hydrochloric acid to pH 7.5 and washed with MTBE. The organic phase was extracted with aqueous 3% sodium bicarbonate solution. The combined aqueous phases were acidified to pH 2 with aqueous 4% hydrochloric acid and extracted with 60 mL of MTBE. This organic phase was washed with brine (1 X 40 mL), dried over sodium sulfate and concentrated. The residue was purified by flash chromatography using 80% hexanes/ethyl acetate (spiked with 0.5% acetic acid). The product (4.2 g, 27 %) was isolated as an off-white solid, mp 89-91°C. Combustion analysis: Found: C 69.50, H 6.04%; $C_{19}H_{20}O_5$ requires C: 69.50, H: 6.14 % 1H NMR (d6-DMSO): δ 12.0, bs, 1H (COOH); δ 11.5, bs, 1H (OH); δ 7.5, t, 2H, (arylH's); δ 7.4, dd, 1H (arylH); δ 7.3, dd, 1H (arylH); δ 7.15, d, 1H (arylH); δ 7.1, t, 1H (arylH); δ 7.0, d, 1H (arylH); δ 6.9, t, 1H (arylH);δ 3.9, t, 2H, (CH_2 α to O); δ 2.05, t, 2H (CH_2 α to COOH); δ1.4, m, 4H (other two CH_2's); δ1.0, p, 2H (CH_2 in middle of chain).

[328] The following compounds were prepared from the appropriate starting materials using the same procedure: Compound 161, Compound 162, Compound 163, Compound 164, Compound 165, Compound 166 and Compound 167.

[329] **(Compound 161) Sodium 8-(2-(2-Hydroxybenzoyl)phenoxy)octanoate:** Starting from 2,2'-dihydroxybenzophenone and ethyl 8-bromooctanoate, the title compound was prepared and then converted into the sodium salt as follows: the free acid (3.56 g, 9.99 mmol) was dissolved in 40 mL of isopropanol, and treated with sodium hydroxide solution (1.7 mL) prepared from of sodium hydroxide (0.90 g, 22.5 mmol) and water (3.7 mL). Isopropanol and MTBE were added causing a solid to precipitate. Heating this mixture caused most of the solid to dissolve. The remaining solids were removed by filtration. The off-white solid that formed upon cooling with dry ice was isolated by filtration and dried under reduced pressure. Combustion analysis: Found: C 65.02%, H 6.22%; $C_{21}H_{23}O_5Na$ requires C 66.00, H 6.65%, ^{1}H NMR (d6-DMSO): δ 12.6, bs, 1H (OH); δ 7.41, t, 1H, (arylH); δ 7.31, t, 1H (arylH); δ 7.27, dd, 1H (arylH); δ 7.15, dd, 1H (arylH); δ 7.03, d, 1H (arylH); δ 6.97, t, 1H (arylH); δ 6.91, d, 1H (arylH); δ 6.65, t, 1H (arylH); δ 3.83, t, 2H, (CH_2 α to O); δ 1.82, t, 2H (CH_2 α to COONa); δ1.3, m, 4H (other two CH_2's); δ1.0, m, 6H (CH_2's in middle of chain). ^{13}C NMR (d6-DMSO): 198.59, 177.35, 161.35, 156.10, 134.56, 131.98, 131.78, 129.55, 128.57, 123.57, 120.18, 118.00, 117.09, 112.51, 67.74, 37.87, 28.83, 28.35, 28.27, 25.84, 24.87.

[330] **(Compound 162) 5-(2-(2-Hydroxybenzoyl)-4-methoxyphenoxy)valeric acid (major isomer data reported):** LC-MS analysis: m + 1 peak confirmed (345). 1H NMR Analysis: (d6-DMSO): δ 12.4, bs, 1H (COOH); δ 11.9, bs, 1H (OH); δ 7.47, t, 1H, (arylH); δ 7.26, dd, 1H (arylH); δ 7.14, d, 1H (arylH); δ 7.13, d, 1H (arylH); δ 7.03, t, 1H (arylH); δ 6.49, d, 1H (arylH); δ 6.42, dd, 1H (arylH); δ 3.95, t, 2H, (CH_2 α to O); δ 3.79, s, 3H, (CH_3O); δ 2.07, t, 2H (CH_2 α to COOH); δ1.48, p, 2H (CH_2 in chain); δ1.34, p, 2H (CH_2 in chain). ^{13}C NMR (d6-DMSO): 199.60, 174.18, 165.97, 163.34, 155.14, 135.14, 131.77, 128.29, 127.83, 120.46, 114.06, 112.69, 107.41, 100.70, 67.51, 55.76, 33.05, 27.80, 20.77.

[331] **(Compound 163) 5-(2-(2-Hydroxybenzoyl)phenoxy)valeric acid:** LC-MS analysis: m + 1 peak confirmed (315). 1H NMR Analysis: (d6-DMSO): δ 11.9, bs, 1H (COOH); δ 11.5, bs, 1H (OH); δ 7.50, dt, 1H, (arylH); δ 7.48, dt, 1H, (arylH); δ 7.35, dd, 1H (arylH); δ 7.25, dd, 1H (arylH); δ 7.14, d, 1H (arylH); δ 7.06, t, 1H (arylH); δ 6.96, d, 1H (arylH); δ 6.85, t, 1H (arylH); δ 3.93, t, 2H, (CH_2 α to O); δ 2.06, t, 2H (CH_2 α to COOH);

δ1.42, p, 2H (CH_2 in chain); δ1.29, p, 2H (CH_2 in chain). ^{13}C NMR (d6-DMSO): 200.59, 174.15, 160.43, 155.71, 135.94, 132.69, 132.22, 128.58, 128.02, 121.50, 120.46, 119.06, 117.30, 112.67, 67.50, 33.05, 27.75, 20.70.

[332]**(Compound 164) 5-(2-(2-Hydroxy-5-methoxybenzoyl)-4-methoxyphenoxy)valeric acid:** LC-MS analysis: m + 1 peak confirmed (375). 1H NMR Analysis: (d6-DMSO): δ 12.4, bs, 1H (COOH); δ 12.0, bs, 1H (OH); δ 7.25, d, 1H, (arylH); δ 7.21, d, 1H, (arylH); δ 6.66, d, 1H (arylH); δ 6.62, dd, 1H (arylH); δ 6.48, d, 1H (arylH); δ 6.42, dd, 1H (arylH); δ 3.96, t, 2H, (CH_2 α to O); δ 3.81, s, 3H, (CH_3O); δ 3.80, s, 3H, (CH_3O); δ 2.08, t, 2H (CH_2 α to COOH); δ1.48, p, 2H (CH_2 in chain); δ1.34, p, 2H (CH_2 in chain). ^{13}C NMR (d6-DMSO): 198.85, 174.20, 165.62, 164.14, 162.54, 157.11, 135.18, 130.22, 120.60, 114.44, 107.04, 105.51, 100.63, 99.24, 67.55, 55.69, 55.48, 33.06, 27.75, 20.77.

[333] **(Compound 166) 4-(2-(2-Hydroxybenzoyl)phenoxy)butyric acid:** LC-MS analysis: m + 1 peak confirmed (333). 1H NMR Analysis: (d6-DMSO): δ 12.0, bs, 1H (COOH); δ 7.46, m, 2H (arylH's); δ 7.33, dt, 1H (arylH); δ 7.29, d, 1H (arylH); δ 6.82, t, 1H (arylH); δ 3.77, t, 2H, (CH_2 α to O); δ 1.85, t, 2H (CH_2 α to COOH); δ1.35, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 200.47, 173.92, 160.40, 155.57, 135.97, 132.64, 132.27, 128.64, 128.00, 121.52, 120.56, 119.10, 117.34, 112.62, 66.99, 29.55, 23.92.

[334] **(Compound 167) 4-(2-Chlorobenzoyl-4-methylphenoxy)butyric acid:** LC-MS analysis: m + 1 peak confirmed (333). 1H NMR Analysis: (d6-DMSO): δ 12.4, bs, 1H (COOH); δ 12.0, bs, 1H (OH); δ 7.23, d, 1H (arylH, *o* to O); δ 3.74, t, 2H, (CH_2 α to O); δ 2.25, s, 3H, CH_3); δ 1.84, t, 2H (CH_2 α to COOH); δ1.33, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 198.76, 173.97, 165.63, 164.10, 162.58, 156.99, 135.11, 130.29, 120.55, 114.45, 107.14, 105.67, 100.67, 99.16, 67.03, 55.69, 55.50, 29.56, 23.85.

Example Preparation of Compounds 168-173

[335] **(Compound 168) 4-(2-Benzoyl-5-methoxyphenoxy)butyric acid:** A 100 mL mini-block tube equipped with a magnetic stir bar was charged with 4.56 g (20.0 mmol) of 2-hydroxy-4-methoxybenzophenone, 2.70 mL (3.68 g, 18.9 mmol) of ethyl 4-

bromobutyrate and 40 mL of dimethylformamide (DMF). Potassium carbonate (2.96 g, 21.4 mmol) was added to the clear solution. The reaction mixture was heated to 80C. After stirring for 20 hr at 25C, the clear reaction mixture was diluted with water. The resulting solid was isolated by filtration. This solid was taken up in 30 mL of tetrahydrofuran (THF) and treated with 3.10 g (24.0 mmol) of potassium trimethylsilanoate. The orange solution was stirred for 20 hr at 25C, diluted with aqueous 4% hydrochloric acid to pH 7.5 and washed with MTBE. The organic phase was extracted with aqueous 3% sodium bicarbonate solution. The combined aqueous phases were acidified to pH 2 with aqueous 4% hydrochloric acid and extracted with 60 mL of MTBE. This organic phase was washed with brine (1 X 40 ML), dried over sodium sulfate and concentrated. The resulting solid was purified by trituration using MTBE/hexanes. More of the product was isolated from the mother liquor. LC-MS analysis: m + 1 peak confirmed (315). 1H NMR Analysis: (d6-DMSO): δ 12.0, bs, 1H (COOH); δ 7.6, d, 2H, (phenylH's, *o* to CO); δ 7.56, t, 1H (phenylH, *p* to CO); δ 7.44, t, 2H (phenylH's, *m* to CO); δ 7.35, d, 1H (arylH, *o* to CO); δ 6.64, m, 2H (arylH's, *m* to CO); δ 3.88, t, 2H, (CH_2 α to O); δ 3.82, s, 3H, (CH_3O); δ 1.84, t, 2H (CH_2 α to COOH); δ1.53, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 195.08, 173.91, 163.17, 158.33, 138.84, 132.37, 131.37, 128.67, 128.24, 120.87, 105.87, 99.02, 66.89, 55.53, 29.45, 23.79.

[336] Other delivery agents were made with the same procedure: Compound 169, Compound 170, Compound 171, Compound 172 and Compound 173.

[337] **(Compound 169) 4-(2-Benzoyl-4-chlorophenoxy)butyric acid:** LC-MS analysis: m + 1 peak confirmed (319). 1H NMR Analysis: (d6-DMSO): δ 11.9, bs, 1H (COOH); δ 7.64, d, 2H, (phenylH's, *o* to CO); δ 7.59, t, 1H (phenylH, *p* to CO); δ 7.51, dd, 1H (arylH, *p* to CO); δ 7.45, t, 2H (phenylH's, *m* to CO); δ 7.36, d, 1H (arylH, *o* to CO); δ 7.14, d, 1H (arylH, *m* to CO); δ 3.87, t, 2H, (CH_2 α to O); δ 1.84, t, 2H (CH_2 α to COOH); δ1.53, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 194.37, 173.82, 154.74, 136.96, 133.42, 131.56, 130.05, 128.97, 128.62, 128.29, 124.48, 114.61, 67.38, 29.37, 23.79.

[338] **(Compound 170) 4-(2-Benzoyl-4-bromophenoxy)butyric acid:** LC-MS analysis: m + 1 peak confirmed (363). 1H NMR Analysis: (d6-DMSO): δ 11.9, bs, 1H (COOH); δ 7.6, m, 3H, (arylH's); δ 7.60, t, 1H (phenylH, *p* to CO); δ 7.49, dd, 1H (arylH, *o*

to CO); δ 7.46, t, 2H (phenylH's, *m* to CO); δ 7.09, d, 1H (arylH, *m* to CO); δ 3.89, t, 2H, (CH_2 α to O); δ 1.82, t, 2H (CH_2 α to COOH); δ1.53, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 194.28, 173.81, 155.19, 136.97 134.48, 133.42, 131.06, 130.48, 128.97, 128.62, 115.08, 112.02, 67.33, 29.35, 23.77.

[339] **(Compound 171) 4-(2-(2-Chlorobenzoyl-5-methylphenoxy)butyric acid:** LC-MS analysis: m + 1 peak confirmed (333). 1H NMR Analysis: (d6-DMSO): δ 12.0, bs, 1H (COOH); δ 7.54, d, 1H, (arylH); δ 7.4, m, 2H (arylH's); δ 7.33, dt, 1H (arylH); δ 7.29, d, 1H (arylH); δ 6.86, m, 2H (arylH's, *o* to O); δ 3.77, t, 2H, (CH_2 α to O); δ 2.31, s, 3H, CH_3); δ 1.85, t, 2H (CH_2 α to COOH); δ1.35, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 193.31, 173.81, 158.34, 145.98, 141.38, 130.99, 130.56, 129.48, 129.43, 128.38, 127.00, 123.95, 121.46, 113.43, 66.95, 29.65, 23.70, 21.48.

[340] **(Compound 172) 4-(2-(2-Chlorobenzoyl-4-methylphenoxy)butyric acid:** LC-MS analysis: m + 1 peak confirmed (333). 1H NMR Analysis: (d6-DMSO): δ 11.95, bs, 1H (COOH); δ 7.43, m, 3H, (arylH's); δ 7.34, m, 3H (arylH's); δ 6.92, d, 1H (arylH, *o* to O); δ 3.74, t, 2H, (CH_2 α to O); δ 2.25, s, 3H, CH_3); δ 1.84, t, 2H (CH_2 α to COOH); δ1.33, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 193.92, 173.81, 156.15, 140.95, 135.37, 131.24, 130.40, 129.65, 129.56, 129.49, 128.62, 127.02, 126.45, 112.95, 67.07, 29.65, 23.75, 19.80.

[341] **(Compound 173) 4-(2-Benzoyl-4-chloro-5-methylphenoxy)butyric acid:** LC-MS analysis: m + 1 peak confirmed (333). 1H NMR Analysis: (d6-DMSO): δ 11.9, bs, 1H (COOH); δ 7.61, d, 2H, (phenylH's, *o* to CO); δ 7.57, t, 1H (phenylH, *p* to CO); δ 7.44, t, 2H (phenylH's, *m* to CO); δ 7.33, s, 1H (arylH, *o* to CO); δ 7.14, s, 1H (arylH, *m* to CO); δ 3.87, t, 2H, (CH_2 α to O); δ 2.33, s, 3H, CH_3); δ 1.81, t, 2H (CH_2 α to COOH); δ1.49, p, 2H (middle CH_2 in chain). ^{13}C NMR (d6-DMSO): 194.31, 173.83, 154.78, 139.80, 137.39, 133.17, 128.91, 128.84, 128.51, 127.55, 124.69, 115.57, 67.32, 29.37, 23.80, 20.03.

Alternative Preparation of Compound F

[342] **Compound F** can alternately be prepared according to Friedel-Crafts acylation of aromatic compounds:

[343] Taking the appropriate substituted phenol, and mixing it with the appropriate Bromoester, using K_2CO_3 as the base, reacting the product with the appropriate aromatic acid chloride in the presence of $AlCl_3$; or Taking the appropriate substituted salicylic acid, and mixing it with the appropriate Bromoester, using K_2CO_3 as the base. The product is converted to an acid chloride $SOCl_2$, which is than reacted with the appropriate substituted benzene in the presence of $AlCl_3$.

Example 8 Preparation of Compound 174

[344] **Compound 174** was prepared in three steps:

A. O-Acetyl-5-chlorosalicylic acid

10 g (57.9 mmol) 5-chlorosalicylic acid was weighed in a 100-mL round-bottomed flask, followed by the addition of acetic anhydride (12.8 mL, 115.9 mmol). The mixture was stirred for 5 minutes before adding concentrated sulfuric acid (2 drops). The reaction was refluxed for 3 hours. Progress of the reaction was monitored by HPLC. The reaction mixture was cooled to room temperature and poured into a beaker containing 2N HCl (200 mL) to precipitate the product out. The product was collected via vacuum filtration. A purity check by HPLC revealed the presence of impurities. The precipitate was stirred in water (150 mL) overnight in a 200-mL round-bottomed flask. The insoluble solid was collected via vacuum filtration. An impurity check by HPLC revealed that the crude product was free of the impurities. The product was dried overnight in vacuo to yield 12 g of O-acetyl-5-chlorosalicylic acid (56 mmol, 97% yield)

B. O-acetyl-5-chlorosalicoyl chloride

Thionyl chloride (~100mL) was charged to a 250-mL round-bottomed flask and was stirred in an ice bath for 15 minutes. O-acetyl-5-chlorosalicylic acid (6.0 g, 27.9 mmol) was slowly added to the cooled thionyl chloride. DMF (2 drops) was added to the reaction mixture to aid in the dissolution of the acid. The reaction was stirred overnight to yield a homogenous solution. Excess thionyl chloride was distilled off in vacuo. The remaining residue was dried in vacuo overnight.

C. 3-(N-2-hydroxy-5-chlorobenzoyl)aminopropionic acid

β-Alanine (2.5 g, 28.0 mmol) was weighed in a 250-mL round-bottomed flask. Methylene chloride (100 mL) was added into the flask and the mixture was stirred for 5 minutes. Chlorotrimethylsilane (6.06 g, 55.7 mmol) was added dropwise to the flask. The reaction was heated to reflux for 1.5 hours. The mixture was allowed to cool to room temperature and was placed in an ice bath for 15 minutes. Triethylamine (8.5 g, 84.0 mmol) was slowly added to the cooled flask. O-Acetyl-5-chlorosalicoyl chloride (7.6 g, 27.9 mmol) was dissolved in methylene chloride (30 mL) and added to the reaction over 0.5 hours. The reaction was stirred overnight, and allowed to warm to room temperature. Progress of the reaction was confirmed by HPLC. The solvent was evaporated in vacuo. The remaining residue was stirred in 2N NaOH (~100 mL) for 2 hours and was slowly heated to 60° C. The solution was cooled to room temperature and then filtered by gravity filtration. The filtrate was slowly acidified with concentrated HCl until precipitates formed. The crude product was collected when the mixture was at pH 6. The product was recrystallized using MeOH-H2O. Purity check by HPLC revealed the presence of impurities. The product underwent several purification and recrystallization steps until a pure compound was obtained. The final product was stirred overnight in methylene chloride, collected by filtration, and dried under vacuum overnight to yield a pale pink powder (3.98 grams, 16.3 mmol, 58.5% yield); mp 181-183 oC; 1HNMR (DMSO-d6) □ 2.47-2.58 (t, 2H), 3.44-3.54 (q, 2H), 6.93-6.98 (d, 1H), 7.39-7.44 (dd, 1H), 7.91-7.96 (d, 1H), 8.93-9.01 (t, 1H), 12.1-12.3 (s, 1H). KF value= 1.615%. Analysis for calculated C10H10NO4Cl*0.2220H2O: C, 48.50, H, 4.25, N, 5.66. Found: C, 48.20; H, 4.03; N, 5.43.

Example 9 Preparation of Compound 175-178

[345] **Compound 175 - 4-(2-Benzyloxy-phenoxy)-butyric acid:**

[346] To a 250 mL flask, equipped with a reflux condenser, magnetic stirrer, and under inert atmosphere, was added 2-benzyloxy-phenol (8.0 g, 40 mmol), 4-bromobutanoic acid ethyl ester (5.7 mL, 40 mmol), potassium carbonate (7.2 g, 52 mmol), and ethanol (100 mL). The reaction mixture was heated to reflux with stirring for 8 hours. The reaction was cooled to room temperature and the insoluble byproduct was removed by suction filtration. 2N aqueous sodium hydroxide (30 mL) was added to the filtrate. This

solution was heated to 50°C for 2 hours. The solution was cooled to room temperature, the ethanol removed under reduced pressure, and the resulting solution was adjusted to pH 9. The aqueous solution was washed with ethyl acetate (2 X 30 mL) and residual ethyl acetate was removed under reduced pressure. The solution was cooled to 0°C with an external ice bath and then acidified to pH 2 with 6N aqueous hydrochloric acid. The precipitated product was collected by suction filtration and dried under vacuum. The product (7.2 g, 63%) was isolated as a white powder. 1H-NMR (400MHz, DMSO-d6): δ 12.0, s, 1H (COOH); δ 7.4, multiplet, 5H (Benzylic aryl H's); δ 7.0, multiplet, 2H (Aryl H's); δ 6.9, multiplet, 2H (Aryl H's); δ 5.0, s, 2H (Benzylic CH2); δ 4.0, t, 2H (CH2 α to phenoxy); δ 2.4, t, 2H (CH2 α to COOH); δ 1.9, multiplet, 2H (remaining CH2 group).

[347] **Compound 176** - (4-Benzyloxy-phenoxy)-acetic acid was purchased from Lancaster.

[348] **Compound 177** - 11-(2-Benzyloxyphenoxy)undecanoic acid:

[349] To a 250 mL Erlenmeyer flask was added freshly ground potassium hydroxide (4.2 g, 74.91 mmol) and 100 mL dimethyl sulfoxide. 2-benzyloxy-phenol (5 g, 24.97 mmol) and 11-bromoundecanoic acid methyl ester (7 g, 25.07 mmol) was added and the mixture was allowed to stir at room temperature overnight. Water (75 mL) was added and the solution was heated to 85°C , with stirring, for 3 hours. The reaction was cooled to room temperature and acidified with concentrated hydrochloric acid to pH 2. The acidified solution was cooled to 4°C for 2 hours, and the precipitate then collect by suction filtration. The product was recrystallized form ethanol/water. The product (8.88 g, 93%) was isolated as a light brown solid, mp 62-63°C. Combustion analysis: Found: C 74.71 H 8.08%; $C_{24}H_{32}O_4$ requires C 74.97, H 8.39 %;

[350] **Compound 178** - 5-(4-Benzyloxy-phenoxy)-pentanoic acid:

[351] To a 500 mL 3-neck flask equipped with a reflux condenser and under inert atmosphere, was added 4-benzyloxy-phenol (30.64 g, 150 mmol), 5-bromopentanoic acid ethyl ester (31.99 g, 150 mmol), potassium carbonate (22.80 g, 165 mmol), and 270 mL of 2-butanone. The reaction mixture was heated to reflux for 23 hours, cooled, and then diluted with ethyl acetate (150mL) and extracted against water (500 mL). The organic layer was washed with water (1 X 250 mL) and brine (1 X 250 mL) and the solvent removed under

reduced pressure. The resulting oil was dried under vacuum for 4 days, during which time a white crystals formed. The white crystals were dissolved in ethyl acetate (100 mL), washed with aqueous 1N sodium hydroxide (3 X 50 mL), and the solvent removed under reduced pressure. The resulting oil was dried under vacuum overnight to produce white crystals. The product was recrystallized from 1:1 ethanol:water and collected by suction filtration and dried under vacuum. This product was used without further purification.

[352] To a 1 L round bottom flask, equipped with a reflux condenser, was added 5-(4-Benzyloxy-phenoxy)-pentanoic acid ethyl ester (15.13 g, 46 mmol) and 2N aqueous sodium hydroxide (47 mL). The mixture was allowed to stir for 30 minutes. Water (200 mL) was added. The mixture was stirred for 20 minutes then heated to reflux for 2 hours to form a brown solution. The solution was quickly cooled to room temperature by the addition of ice. The cooled solution was acidified with 2N aqueous hydrochloric acid (50 mL) and the resulting white precipitate was collected by suction filtration, washed with water (2 X 100 mL), hexanes (2 X 100 mL), and dried under vacuum over night. The powder was finely ground and washed with hexanes (1 X 250 mL) and diethyl ether (1 X 250 mL) to yield a white powder. This powder was dissolved in a mixture of ethyl acetate (300 mL) and diethyl ether (200 mL) in a 1 L beaker. The solution was heated for 10 minutes, methanol (5 mL) added, heated an additional 10 minutes, and then filtered through a Celite plug to yield a clear yellow solution. The product was crystallized by slow addition of hexanes. The first crop of crystals was collected by filtration and hexanes (200 mL) was added to the mother liquor. The solution was then concentrated under reduced pressure to a volume of 400 mL and allowed to rest. The second batch of crystals was collected by filtration and combined with the first. The product (8.92 g, 65%) was isolated as a white crystalline material, mp 127-128°C. Combustion analysis: Found: C 71.01 H 6.98%; $C_{18}H_{20}O_4$ requires C 71.98, H 6.71 %;

Compound Sequence	HPLC Retention Time	KF Value	Melting Point Range Value	CHNC C	CHNC H	CHNF C	CHNF H
175	5.93 min						
176	5.54	0		69.76	5.46		
176	5.54	0		69.76	5.46		
177	9.19	0	62-63	74.97	8.39	74.71	8.08
178	6.12	0	127-128	71.98	6.71	71.01	6.98

Example 10- Solid Oral Delivery of PYY[3-36] in Rats

[353] PYY[3-36] stock solution (80 mg/ml) prepared with deionized water was used (PYY available from Bachem California Inc. of Torrance, CA).

[354] About 0.08 mg/tablet (about 0.3 mg/kg) of PYY (about 1 µl) was added and blended with either about 13.5 or 27 mg/tablet (50 or 100 mg/kg) of the free acid or sodium salt of the Delivery Agent Compound, as indicated below. Upper punch, lower punch and die of Carver 4350 manual pellet press with a Caplet shape model sold by Natoli Engineering Company, Inc. (St. Charles, Missouri) were treated with magnesium stearate (0.1%). About 13.58 or about 27.08 mg of mixed powder was fed into the die and a mini bead shape tablet was made at about 1000 psi bar pressure. The resulting solid dosage form is about the size of a standard capsule size 9 (about 2.65 mm diameter and about 8.40 mm length) for the 27.08 mg size and about 2.65 mm diameter and about 4.20 mm length for the 13.58 mg solid.

[355] Male Sprague Dawley rats (about 260 to about 280 g) were fasted overnight and then anesthesized by standard CO_2 inhalation technique for about 10 to 30 seconds resulting in an anesthesized state for about less then one minute, preferably about 10 to about 30 seconds.

[356] An oral dosing tube was used. The dosing tube was inserted into the rat's mouth and carefully threaded down the rats pharynx and esophagus about 8 cm to about 15 cm depending on the weight of the rat (typically about 11 cm). The solid dosage form was delivered into the distal esophagus and/or stomach by pressing the plunger of the oral dosing tube.

[357] Blood samples were collected retro-orbitally typically at time = 0, 15, 30, 60 and 90 minutes. Serum PYY concentrations were quantified using a PYY[3-36]

radioimmunoassay (Catalog #RK-059-02 from Phoenix Pharmaceuticals, Inc., Belmont, CA). Results from the animals in each group were averaged for each time point. The maximum of these averages (i.e., the mean peak serum PYY[3-36] concentration ± standard deviation (SD)) is reported below.

Table 1. PYY(3-36) Oral administration in rats.

Delivery Agent Compound	Method of Administration	Compound dose (mg/kg)	PYY(3-36) dose (mg/kg)	Mean serum peak of PYY (pg/ml) ± SD
23 - sodium salt	Oral, solid dose, 1 tablet per animal	100	0.3	427.4 ± 258.7
121 - sodium salt	Oral, solid dose, 1 tablet per animal	100	0.3	897.1 ± 257.3
121 - free acid	Oral, solid dose, 1 tablet per animal	50	0.3	161.7 ± 148.5
174 - sodium salt	Oral, solid dose, 1 tablet per animal	100	0.3	675 ± 427.1
174 - free acid	Oral, solid dose, 1 tablet per animal	100	0.3	0

Example 11 PYY[3-36] Liquid Oral Delivery in Rats

[358] Oral gavage (PO) dosing solutions of delivery agent compound and Peptide YY residues 3-36 (PYY[3-36]) (available from Bachem California Inc. of Torrance, CA) in deionized water were prepared as follows.

[359] PYY [3-36] stock solution (80 mg/ml) was prepared with deionized water. Oral dosing compositions containing 200 mg/kg of delivery agent compound and 0.3 mg/kg of PYY in aqueous solution were prepared. A solution of the compound 23 is made with one equivalent to sodium hydroxide to convert the free acid delivery agent to its sodium salt.

[360] Male Sprague-Dawley rats weighing between 240-320 g were fasted up to a maximum 24 hours before the experiments and administered ketamine (44 mg/kg) and thorazine (1.5 mg/kg) by intramuscular injection before the test article administration. Afterwards, the anesthetized animals were administered the test article by oral gavage. A dosing group of five animals was administered one of the dosing solutions. For oral gavage

(PO), an 11 cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. The dosing solution was administered by pressing the syringe plunger.

[361] Blood samples were collected serially from the tail artery, or by cardiac puncture, typically at time = 0, 15, 30, 45, 60 and 90 minutes. Serum PYY concentrations were quantified using a PYY[3-36] radioimmunoassay (Catalog #RK-059-02 from Phoenix Pharmaceuticals, Inc., Belmont, CA). Results from the animals in each group were averaged for each time point. The maximum of these averages (i.e., the mean peak serum PYY[3-36] concentration ± standard deviation (SD)) is reported below in Table 2. No significant PYY[3-36] was detected in blood when the animals were dosed orally with PYY[3-36] alone.

Table 2. PYY(3-36) Oral administration (Liquid) in rats.

Compound	Method of Administration	Compound dose (mg/kg)	PYY(3-36) dose (mg/kg)	Mean serum peak of PYY (pg/ml) ± SD
23	Oral (liquid dose)	200	0.3	788.198 ± 50.59
151	Oral (liquid dose)	200	0.3	801.96 ± 290.61
158	Oral (liquid dose)	200	0.3	1065 ± 75.352
160	Oral (liquid dose)	200	0.3	370.39 ± 306.29
160	Oral (liquid dose)	200	0.3	631.96 ± 316.16
160	Oral (liquid dose)	200	0.3	705.106 ± 75.906
161	Oral (liquid dose)	200	0.3	340.95 ± 228.946
174	Oral (liquid dose)	200	0.3	1262.26 ± 313.58

Example 12 –Human Recombinant Insulin Oral Delivery in Rats

[362] Insulin (human recombinant) was obtained from ICN Biomedicals (Aurora, OH) as a bulk powder. To prepare stock solutions, insulin was dissolved in deionized water (pH~6.5) to obtain a concentration of 15 mg/ml. Stock solutions were kept

frozen at -20°C in 1.0-ml aliquots until used. For dosing solutions, the delivery agent compound was dissolved in deionized water to obtain a final concentration of 200 mg/ml. The free acid form of delivery agent was converted to the sodium salt by adding one equivalent of sodium hydroxide. Solutions were vortexed, sonicated, and heated, and if necessary, additional sodium hydroxide was added in μl quantities to achieve uniform solubility. Solutions were adjusted to a pH of 3.5-8.5 by the addition of either hydrochloric acid or sodium hydroxide. Insulin stock (typically 66.7 μls) was then added to the delivery agent solution to obtain a final concentration of 0.5 mg/ml. After solubilization and drug addition, solutions were brought to final volume by the addition of deionized water.

[363] Insulin was administered to male, Sprague-Dawley rats either alone or in combination with an Emisphere delivery agent by oral gavage (PO). Typically, rats were fasted for 18-24 hours prior to dosing. For dosing, a Rusch 8 French catheter was cut to 11 cm in length and adapted to fit a 1-ml syringe. The syringe was filled with dosing solution and the catheter was wiped dry of excess solution. The catheter was inserted into the rat mouth and fed down the esophagus (10.0 cm). The dosing solution was delivered by pressing the syringe plunger while holding the rat in an upright position.

Sample collection and handling: Insulin

[364] During blood sampling, rats were exposed briefly (~10 sec) to carbon dioxide until prostrate, immediately prior to each sampling time point. For blood sampling, a 77-mm capillary tube was inserted into the retroorbital sinus. Typically, blood samples were collected prior to dosing (time 0) and at 15, 30, 45, and 60 minutes after dosing. Samples were collected into CAPIJECT® tubes (Terumo Corporation, Tokyo, Japan) containing a clot activator (red top, serum separator tubes). Samples were allowed to clot for ~20 min at 4°C. After clotting, samples were centrifuged at 10,000 rpm for 4 minutes at 6°C in order to separate the serum. Serum was collected into eppendorf tubes and frozen at -20°C until assayed.

Sample collection and handling: Whole blood glucose

[365] In order to determine the pharmacodynamic response, a hand-held glucometer (OneTouch Ultra, LifeScan® (Johnson & Johnson, New Brunswick, New Jersey)) was used to measure whole blood glucose after administration of insulin or insulin and delivery agent. Samples were collected either from the retroorbital sinus (see Sample collection and handling: Insulin) or from the tail artery (i.e. tail clip). For tail clipping, the tip of the tail was severed approximately 5 mm from the tip using a scalpel blade. After discarding the first drop of blood, a small sample (~5-10 µl) was touched to the glucometer test strip (OneTouch Ultra, LifeScan) and a blood glucose reading was generated by the meter. For each subsequent sampling time point, the clot formed at the tip of the tail was broken up and a fresh sample was collected. Typically, samples were collected prior to dosing (time 0) and at 15, 30, 45, and 60 minutes after dosing.

Table 3. Insulin Oral (liquid dose) administration to rats.

Compound	Method of Administration	Delivery Agent Compound dose (mg/kg)	Insulin dose (mg/kg)	Maximum % drop in glucose from control ± SD
24	Oral (liquid dose)	200	0.5	-14.73 ± 17.64
25	Oral (liquid dose)	200	0.5	-14.81 ± 12.99
26	Oral (liquid dose)	200	0.5	-25.93 ± 14.86
27	Oral (liquid dose)	200	0.5	-25.40 ± 30.61
28	Oral (liquid dose)	200	0.5	-11.41 ± 18.92
29	Oral (liquid dose)	200	0.5	-29.25 ± 6.97
140	Oral (liquid dose)	100	1	Cmax = 81.16 ± 114.98 µIU/mL
141	Oral (liquid dose)	100	1	Cmax = 204.05 ± 60.88 µIU/mL
142	Oral (liquid dose)	100	1	Cmax = 118.16 ± 72.75 µIU/mL

145	Intracolonic	50	0.1	Cmax = 15.03 ± 7.80 μIU/mL
145	Oral (liquid dose)	100	1	Cmax = 3.92 ± 5.62 μIU/mL
160	Oral (liquid dose)	200	0.5	Cmax = 74 ± 7.5 μIU/mL
165	Oral (liquid dose)	200	0.5	-33.0
166	Oral (liquid dose)	200	0.5	-5.7
167	Oral (liquid dose)	200	0.5	-21.2
167	Oral (liquid dose)	200	0.5	-17.7
167	Oral (liquid dose)	200	0.5	-26.2
167	Oral (liquid dose)	200	0.5	-17.8
167	Oral (liquid dose)	200	0.5	-22.7

Example 13 - Human Zinc Insulin – Oral Delivery

Oral dosing (PO) compositions of delivery agent compound and human zinc insulin (minimum 26 IU/mg available from Calbiochem – Novabiochem Corp, La Jolla, CA) were prepared in deionized water. 500 mg of delivery agent compound was added to 1.5 ml of water. The free acid of the delivery agent compound was converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide. The solution was vortexed, then heated (about 37°C) and sonicated. The pH was adjusted to about 7 to 8.5 with NaOH or HCl. Additional NaOH was added, if necessary, to achieve uniform solubility, and the pH re-adjusted to about 7 to 8.5. Water was then added to bring the total volume to about 2.4 ml and vortexed. About 1.25 mg insulin from an insulin stock solution (15 mg/ml made from 0.5409 g insulin and 18 ml deionized water, adjusting with HCl and NaOH to pH 8.15 and to obtain a clear solution using 40 ml concentrated HCl, 25 ml 10N NaOH and 50

ml 1N NaOH) was added to the solution and mixed by inverting. The final delivery agent compound dose, insulin dose and dose volume amounts are listed.

Male Sprague-Dawley rats weighing between about 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. For oral dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. The dosing solution was administered by pressing the syringe plunger.

Blood samples were collected serially from the tail artery, typically at time = 15, 30, 60, 120 and 180 minutes. Serum insulin levels were determined with an Insulin ELISA Test Kit (Kit # DSL-10-1600 from Diagnostic Systems Laboratories, Inc., Webster, TX), modifying the standard protocol in order to optimize the sensitivity and linear range of the standard curve for the volumes and concentrations of the samples used in the present protocol. Serum human insulin concentrations (μU/ml) were measured for each time point for each of the five animals in each dosing group. The five values for each time point were averaged and the results plotted as serum insulin concentration versus time. (Previous experiments revealed no measurable levels of human insulin following oral dosing with human insulin alone.) The maximum (peak) and the area under the curve (AUC) are reported below in Table 5. For % change from baseline for Blood Glucose the ONE TOUCH ® (Life Scan, Johnson & Johnson, New Brunswick, New Jersey).

Table 4 - Insulin - Oral Delivery

Delivery Agent Compound	Delivery Agent Compound Dose (mg/kg)	Insulin Dose (mg/kg)	Volume dose (ml/kg)	Cmax(glucose) (μU/ml)	AUC	Glucose (% control)
123	200	0.50		107.3	7440	
125	200	0.50		98.3	7687.5	
123	200	0.50		100.3	7447.5	
115	200	0.50		83.3	3232.5	
116	200	0.50		89.5	3292.5	
118	200	0.50		90.5	4327.5	
124	200	0.50		87.8	1582.5	
134	200	0.50		81.5	3817.5	
136	200	0.50		91.5	4507.5	
138	200	0.50		93.4	6907.5	
124	200	0.50		59.9	112.5	
152	200	0.5				-29.3%
153	200	0.5				-7.1%
154	200	0.5				-7.9%
159	200	0.5				-6.6%
159	200	0.5			9.1	-36.5%

Example 14 - Insulin -- Pulmonary Delivery

Dosing compositions of delivery agent compound and human insulin in water were prepared. Typically, to 1.5 mg of delivery agent compound was added deionized water to bring the volume to 1.0 ml, and the solution was vortexed. Either the sodium salt of the delivery agent compound was used or the free acid was converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide (10 N) and diluting with water. The solution was vortexed, then heated (about 37°C) and sonicated. The pH was adjusted to between about 7.0 to 8.5 with NaOH or HCl. 75 μl human insulin stock solution (2 mg/ml) was added to the solution. (The stock solution was made as follows. To 0.02 g insulin was added 3 ml pH 3.0 HCl solution in deionized water. The pH of the resulting solution was brought to below 3.0 (about 2.6) with HCl and NaOH until the solution was clear. The pH was then raised to 7.6 using NaOH and HCl. The final volume was brought to 10 ml with pH 7.5 deionized water. Final pH 7.59.) Water was then added to bring the total volume to 2.0 ml, and the solution was inverted gently several times. The solution may be used in the dosing protocol immediately, or alternatively, the solution may be placed into a 37°C water bath for one hour prior to dosing. The final delivery agent compound dose, insulin dose and volume dose amounts are listed below in Table 4.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (3.0 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia (using the same amount of ketamine and 1.5 mg/kg chlorpromazine). Typically, a dosing group of five animals was administered one of the dosing solutions. A control group of five animals was dosed insulin alone. A tracheal instillator for rodents, equipped with light (available from Penn Century, Inc., Pittsburgh, PA) was filled with dosing solution and inserted down the throat until the needle went into the trachea (confirmed visually). The dosing solution was administered by pressing the plunger.

Blood samples from each animal were collected serially from the tail artery, typically at 5, 15, 30, 60 and 120 minutes after dosing. Serum insulin levels were determined with an Insulin ELISA Test Kit (Kit # DSL-10-1600 from Diagnostic Systems Laboratories, Inc., Webster, TX), modifying the standard protocol in order to optimize the sensitivity and linear range of the standard curve for the volumes and concentrations of the samples used in the

present protocol. Serum insulin concentrations (μU/ml) were measured for each time point for each of the five animals in each dosing group. The five values for each time point were averaged and the results plotted as serum insulin concentration versus time. The ratio of the area under the curve (AUC) for the test group versus that of the control group is reported below. The ratio of the maximum serum insulin concentration (Cmax) for the test group versus that of the control group is also reported below.

Table 5. Pulmonary Delivery of Insulin

Delivery Agent Compound	Volume dose (ml/kg)	Delivery Agent Compound Dose (mg/kg)	Insulin Dose (mg/kg)	Cmax
174	0.4	16	0.03	18.36 ± 19.18

Example 15 – Oral and Intracolonic Heparin Delivery

[371] Oral gavage (PO) and/or intracolonic (IC) dosing solutions containing a delivery agent compound and heparin sodium USP in 25% aqueous propylene glycol were prepared. The sodium salt of the compound was used. Typically, delivery agent compound and heparin (about 166-182 IU/mg) were mixed by vortex as dry powders. This dry mixture was dissolved in 25% v/v aqueous propylene glycol, vortexed and placed in a sonicator (about 37° C). The pH was adjusted to about 7 (6.5 to 8.5) with aqueous NaOH (2N). The dosing solution was sonicated to produce a clear solution. The final volume was adjusted to 3.0 mL. The final delivery agent compound dose, heparin dose and volume dose amounts are listed below in Table 6.

[372] The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 275-350g were fasted for 24 hours and were anesthetized with ketamine hydrochloride (88 mg/kg) intramuscularly immediately prior to dosing. A dosing group of five rats was administered one of the dosing solutions. For oral gavage (PO) dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 mL syringe with a

pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the rat's incisors. Solution was administered by pressing the syringe plunger. For intracolonic (IC) dosing, a 7.5 cm 8 fr Rusch catheter was adapted to a 1 ml syringe with a pipette tip. The dosing catheter was inserted into the colon through the anus until the tube was no longer visible. The dosing solution was injected slowly into the colon.

[373] Citrated blood samples were collected by cardiac puncture following the administration of ketamine (88 mg/kg), typically at time – 0.25, 0.5, 1.0 and 1.5 hours. Heparin activity was determined by utilizing the activated partial thromboplastin time (APTT) according to the method of Henry, J.B., Clinical Diagnosis and Management by Laboratory Methods, Philadelphia, PA, W.B. Saunders (1979). Previous studied indicated baseline values of about 20 sec. Results from the five rats in each group were averaged for each time point. The maximum is reported below in Table 6.

Table 6. Oral/Intracolonic Delivery of Heparin

Delivery Agent Compound	**Method of Administration**	**volume dose (ml/kg)**	**Compound Dose (mg/kg)**	**Heparin Dose (mg/kg)**	**Mean Peak APTT (sec) ± SD)**	**pH**
114	IC	1	50	25	42.90 ± 8.70	7.61
140	IC	1	50	25	23.49 ± 6.12	7.67
141	IC	1	50	25	52.40 ± 21.54	7.62
143	IC	1	50	25	114.69 ± 121.62	7.18
145	IC	1	50	25	134.42 ± 99.03	6.93
151	PO	3	300	100	252.09 ± 107.13	
151	IC	1	50	25	2.36 ± 1.27 (antifactor Xa)	7.06
151	IC	1	25	25	3.39 ± 3.07 (antifactor Xa)	7.23
160	IC	1	50	25	131 + 154 (Tmax= 90 min)	

Example 16 - Parathyroid Hormone Delivery (PTH 1-34) Oral/ Intracolonic Delivery

[374] Oral gavage (PO) and/or intracolonic (IC) dosing solutions of delivery agent compound and human parathyroid hormone residues 1-34 (PTH) in water were prepared. The sodium salt of the delivery agent compound was used. Typically, a solution of the compound was prepared in water and stirred, adding one equivalent of sodium hydroxide (1.0 N) when making sodium salt. The final dosing solutions were prepared by mixing the compound with a PTH stock solution (PTH obtained from Eli Lilly and Co., Indianapolis, IN) (typically having a concentration of 5 mg PTH/ml) and diluting to the desired volume (usually 3.0 ml). The final compound, PTH and volume dose amounts are listed below in Table 7.

[375] The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. A dosing group of five rats was administered one of the dosing solutions. For oral gavage (PO) dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 mL syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the rat's incisors. Solution was administered by pressing the syringe plunger. For intracolonic (IC) dosing, a 7.5 cm Rusch catheter tube (French 8 or 6) was adapted to a syringe with an Eppendorf pipette tip. The syringe was filled with the dosing solution by drawing the solution through the catheter tube. The catheter tube was wiped dry. K-Y jelly was applied to the tip, avoiding contact with the eye of the tube, and the tube was inserted into the colon through the anus until the tube was no longer visible. The solution was injected by pressing the syringe plunger, and the tube was removed.

[376] Blood samples were collected serially from the tail artery, typically at time = 0, 15, 30, 45, 60 and 90 minutes for oral and 0, 10, 20, 30, 60 and 90 for IC dosing. Serum PTH concentrations were quantified by an PTH radioimmunoassay kit (Kit # RIK 6101 from Peninsula Laboratories, Inc. San Carlos, CA). Previous studies indicated baseline values of about zero. Results from the five rats in each group were averaged for each time point. The maximum is reported below in Table 7.

Table 7. Oral/Intracolonic Delivery of PTH in Rats

Delivery Agent Compound	Method of Admini-stration	volume dose (ml/kg)	Compound Dose (mg/kg)	PTH Dose (ug/kg)	Mean Peak Serum [PTH] (pg/ml) ± SD	pH
113	Oral	1	100	200	780.77 ± 439.92	8.18
113	Oral	1	100	200	53.51 ± 39.55	8.09
114	Oral	1	100	200	135.78 ± 136.97	8.41

Example 17 Interferon – Oral Delivery

[377] Dosing solutions of delivery agent compound and interferon alfacon-1 (IFN) (available as Infergen® from InterMune, Inc. of Brisbane, CA) were prepared in deionized water. The free acid of the delivery agent compound was converted to the sodium salt with one equivalent of sodium hydroxide. Typically, a solution of the delivery agent compound was prepared in water and stirred, adding one equivalent of sodium hydroxide (1.0 N) when making the sodium salt. This mixture was vortexed and placed in a sonicator (about 37°C). The pH was adjusted to about 7.0 to 8.5 with aqueous NaOH. The mixture was vortexed to produce a uniform suspension or solution, also using sonication and heat if necessary. Additional NaOH was added, if necessary, to achieve uniform solubility, and the pH re-adjusted to about 7.0 to 8.5. The delivery agent compound solution was mixed with an IFN stock solution (about 22.0 to 27.5 mg/ml in phosphate buffered saline) and diluting to the desired volume (usually 3.0 ml). The final delivery agent compound and IFN doses, and the dose volumes are listed below in Table 8.

[378] The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. An 11cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. The dosing solution was administered by pressing the syringe plunger.

[379] Blood samples were collected serially from the tail artery, typically at time = 0, 15, 30, 45, 60 and 90 minutes. Serum IFN concentrations were quantified using Cytoscreen Immunoassay Kit for human IFN-alpha (catalog # KHC4012 from Biosource International, Camarillo, CA). Previous studies indicated baseline values of about zero. Results from the animals in each group were averaged for each time point. The maximum of these averages (i.e., the mean peak serum IFN concentration) is reported below in Table 8.

Table 8. Interferon - Oral Delivery

Delivery Agent Compound	Delivery Agent Compound Dose (mg/kg)	IFN Dose (mg/kg)	Volume dose (ml/kg)	Mean Peak Serum [IFN] (ng/ml) ± SD	pH
141	200	1	1	0.73 ± 0.44	8.29
147	200	1	1	1.27 ± 0.60	8.45
174	200	1	1	0.5 ± 0.57	
174	200	1	1	0.18 ± 0.17	
174	200	1	1	3.96 ± 2.72	
174	200	1	1	17.4 ± 9.12	

Example 18 – Oral Delivery of Salmon Calcitonin (sCT)

[380] Oral dosing (PO) compositions of delivery agent compound and salmon calcitonin (sCT) in water were prepared. Typically 450 mg of delivery agent compound was added to 2.0 mL of water. Either the sodium salt of the compound was used or the free acid was converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide (1.0 N) and diluting with water. The solution was vortexed, then heated (about 37° C) and sonicated. The pH was adjusted to about 7 (6.5 to 8.5) with NaOH or HCl. 90 µg sCT from a stock solution was added to the solution. Water was then added to bring the total volume to about 3.0 mL (varies depending on solubility of the delivery agent compound). The final delivery agent compound dose, sCT dose and volume dose amounts are listed below in Table 9.

[381] Male Sprague-Dawley rate weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. A dosing group of five rats was administered one of the dosing solutions. For oral dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 mL syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1

cm of tubing past the rat's incisors. Solution was administered by pressing the syringe plunger.

[382] Blood samples were collected serially from the tail artery, typically at time = 0, 10, 20, 30, 60 and 90 minutes. Serum sCT was determined by testing with a EIA kit (Kit # EIAS-6003 from Peninsula Laboratories, Inc., San Carlos, CA) modifying the standard protocol from the kit as follows: incubated with 50 µl peptide antibody for 2 hours with shaking in the dark, washed the plate, added serum and biotinylated peptide and diluted with 4 mL buffer, and shook overnight in the dark. Numbers were adjusted according to baseline values obtained at time = 0. The results from the five rats in each dosing group were averaged for each time point. The maximum is reported below in Table 9.

Table 9 Oral delivery of Salmon Calcitonin (sCT)

Delivery Agent Compound	Volume Dose (ml/kg)	Compound Dose (mg/kg)	sCT Dose (µg/kg)	Mean Peak Serum Sct (pg/ml ± SD) (SE)
174	150	30	1	182.83 + 184.82
174	150	30	1	198.21 + 205.15
174	150	30	1	70.81 + 118.47

Example 19 – Oral/Intracolonic Delivery of Recombinant Human Growth Hormone (rhGH)

[383] Oral gavage (PO) and/or intracolonic (IC) dosing solutions of delivery agent compound and rhGH in phosphate buffer were prepared (rhHG available from Novartis, Basel, Switzerland). The sodium salt of the delivery agent compound was obtained by reacting the free acid with one equivalent of sodium hydroxide. The final dosing solutions were prepared by mixing the compound with an rhGH stock solution (15 mg rhGH/ml) and

diluting to the desired volume (usually 3.0 ml). The compounds and rhGH dose amounts are listed below in Table 10.

[384] The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. A dosing group of five rats was administered one of the dosing solutions. For oral gavage (PO) dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 mL syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the rat's incisors. Solution was administered by pressing the syringe plunger. For intracolonic (IC) dosing, a 7.5 cm Rusch catheter tube (French 8 or 6) was adapted to a syringe with an Eppendorf pipette tip. The syringe was filled with the dosing solution by drawing the solution through the catheter tube. The catheter tube was wiped dry. K-Y jelly was applied to the tip avoiding contact with the eye of the tube, and the tube was inserted into the colon through the anus until the tube was no longer visible. The solution was injected by pressing the syringe plunger, and the tube was removed.

[385] Blood samples were collected serially from the tail artery or retroorbital sinus, typically at time = 0, 15, 30, 45, 60 and 90 minutes for oral and 0, 10, 20, 30, 60 and 90 for IC dosing. Samples were collected into CAPIJECT® tubes (Terumo Corporation, Tokyo, Japan) containing a clot activator (red top, serum separator tubes). Samples were allowed to clot for ~20 min at 4°C. Serum rHGH concentrations were quantified by an rHGH immunoassay test kit (Kit #K1F4015 from Genzyme Corporation Inc., Cambridge, MA). The five samples from each time period were pooled. Previous studies indicated baseline values of about zero.

[386] The maximum concentration for each group is reported below in Table 10.

Table 10. <u>Oral/Intracolonic Delivery of rhGH in Rats</u>

Delivery Agent Compound	Method of Admini-stration	volume dose (ml/kg)	Compound Dose (mg/kg)	rhGH Dose (mg/kg)	Mean Peak Serum Sct (ng/ml)
160	PO	1	200	3	-
161	PO	1	200	3	1.033 (± 2.31) (Tmax = 15 min)
174	PO	1	200	3	57.42

All publications, references, patents, and published patent applications referred to herein are incorporated by reference.

CLAIMS

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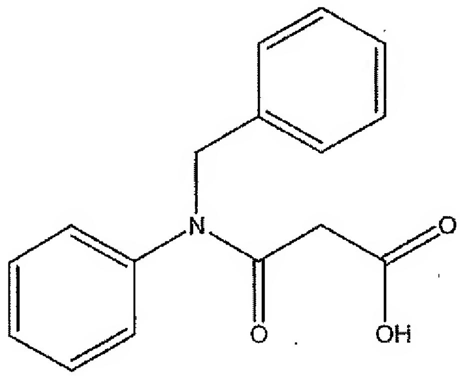

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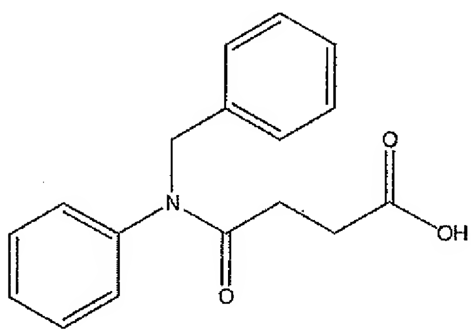

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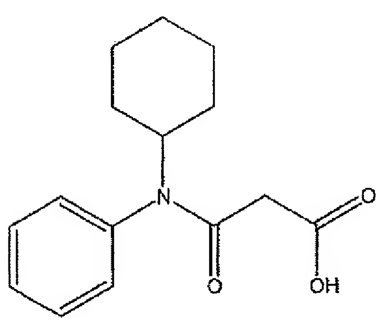

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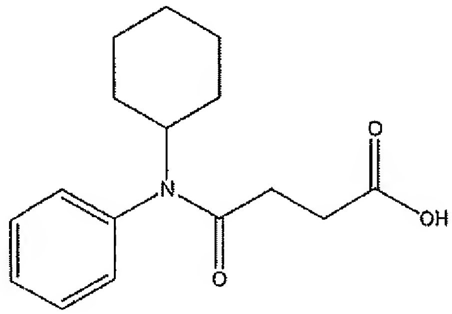

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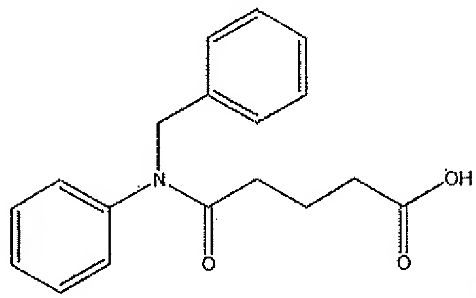

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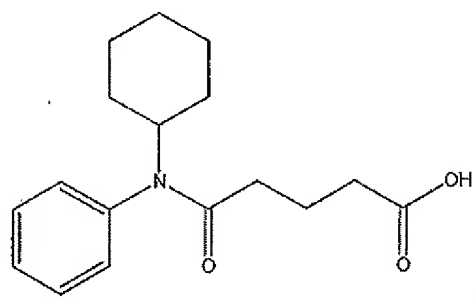

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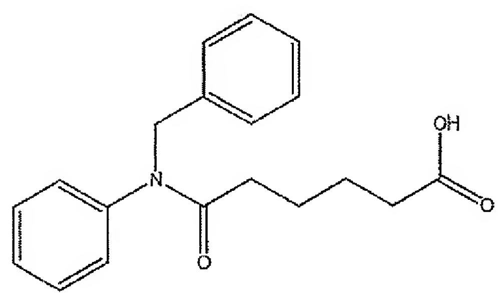

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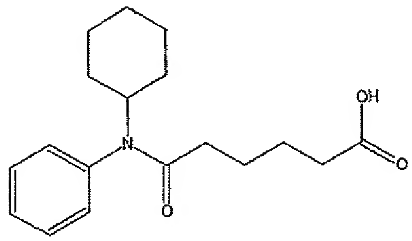

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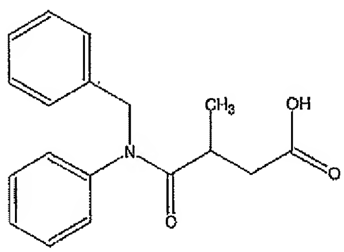

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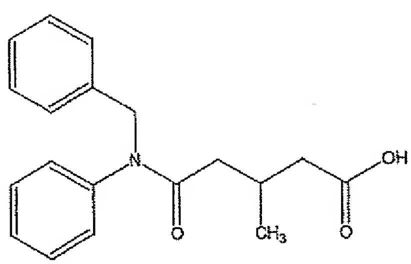

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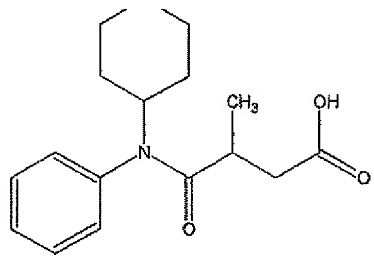

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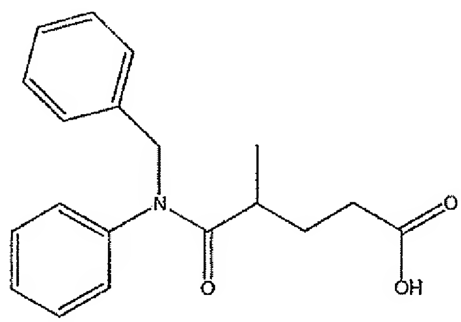

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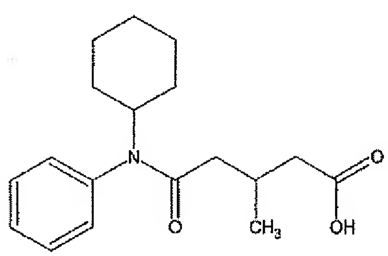

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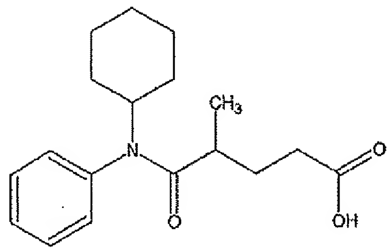

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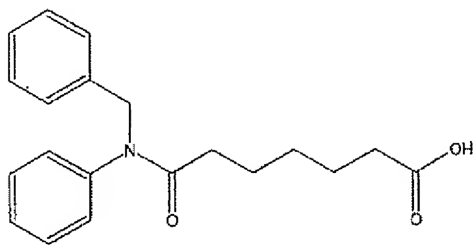

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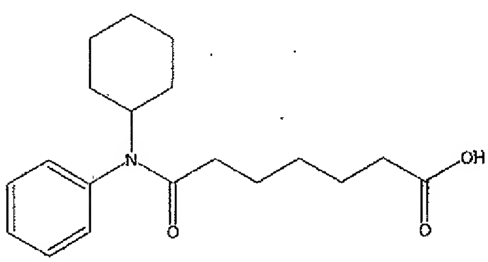

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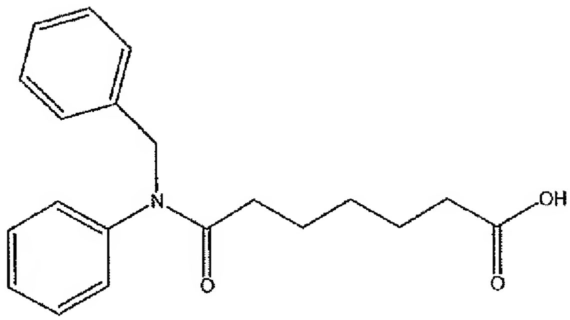

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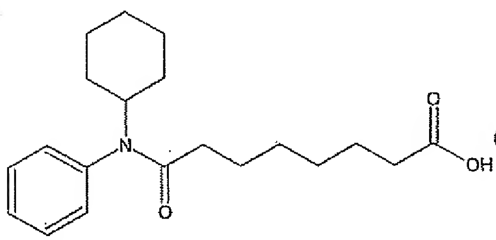

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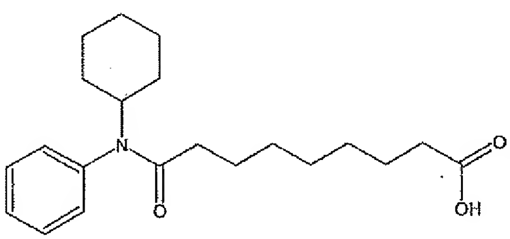

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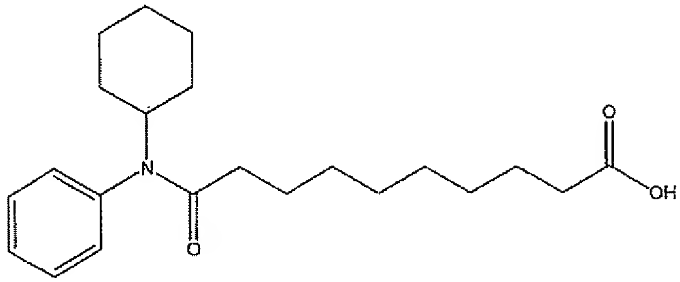

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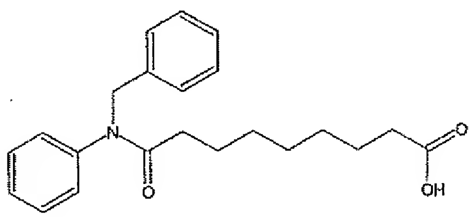

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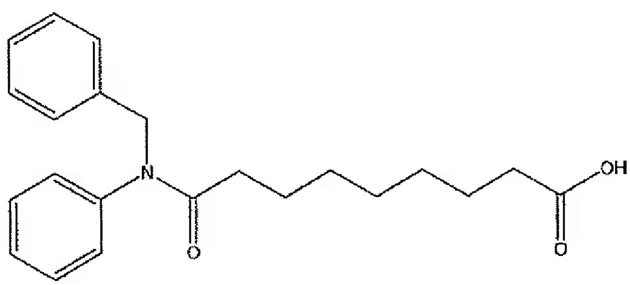


(Compound 22)

and salts thereof.

2. A composition comprising:

(A) at least one active agent; and

(B) a compound of claim 1 .

3. The composition of claim 2, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

4. The composition of defined in claim 2, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

5. The composition of claim 4, wherein said biologically active agent comprises a peptide.

6. The composition of claim 4, wherein said biologically active agent comprises a mucopolysaccharide.

7. The composition of claim 2, wherein said biologically active agent is selected from the group consisting of

Amylin and Amylin Agonists;
Adrenocorticotropin;
Antigens;
Antimicrobials, including Antibiotics, Anti-Bacterials and Anti-Fungal Agents; non-limiting examples of Antibiotics include Gram-Positive Acting, Bacteriocidal, Lipopeptidal and Cyclic Peptidal Antibiotics, such as Daptomycin And Analogs thereof;
Anti-Migraine Agents such as BIBM-4096BS And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;
Antivirals including Acyclovir, Valacyclovir;
Atrial Naturetic Factor;

Bisphosphonates, including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;
Calcitonin, including Salmon, Eel, Porcine And Human;
Cholecystokinin (CCK) And CCK Agonists Including CCK-8;
Cromolyn Sodium (Sodium Or Disodium Chromoglycate);
Cyclosporine;
Desferrioxamine (DFO);
Erythropoietin;
Exedin and Exedin Agonists, including Exendin-3, Exendin-4;
Filgrastim
Follicle Stimulating Hormone (recombinant and natural);
Glucagon-Like Peptide 1 (GLP-1), Glucagon, and Glucagon-Like Peptide 2 (GLP-2);
Glucocerebrosidase;
Gonadotropin Releasing Hormone;
Growth Hormone Releasing Factor;
Growth Hormone Releasing Hormones;
Growth Hormones, Including Human Growth Hormones (hGH), Recombinant Human Growth Hormones (rhGH), Bovine Growth Hormones, And Porcine Growth Hormones;
Heparin, Including Unfractionated Heparin, Heparinoids, Dermatans, Chondroitins, Low Molecular Weight Heparin, Very Low Molecular Weight Heparin Ultra Low Molecular Weight Heparin and synthetic heparins including Fondiparinux;

Insulin, Including Porcine, Bovine, Human, And Human Recombinant, Optionally Having Counter Ions Including Zinc, Sodium, Calcium And Ammonium;
Insulin-Like Growth Factor, Including IGF-1;
Interferons, Including α (E.G., Interferon Alfacon-1 (Available As Infergen® From Intermune, Inc. Of Brisbane, Ca)), β, OMEGA and γ;
Interleukin-1; Interleukin-2; Interleukin-11; Interleukin-21;
Leutinizing Hormone and Leutinizing Hormone Releasing Hormone;
Leptin (OB Protein);
Monoclonal Antibodies including Retuxin, TNF-alpha soluble receptors;
Oxytocin;
Parathyroid Hormone (PTH), Including Its Fragments, including PTH 1-34 and PTH 1-38;
Peptide YY (PYY) Including PYY Agonists, Fragment 3-36;
Prostaglandins;
Protease Inhibitors;
Somatostatin;
Thrombopoietin;
Vancomycin;
Vasopressin;
Vitamins;
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;

or any combination thereof.

8. The composition of claim 7, wherein said biologically active agent comprises a human growth hormone, interferon, insulin, heparin, low molecular weight heparin, cromolyn sodium, PYY, an anti-microbial agent, calcitonin, parathyroid hormone, erythropoietin, and combinations thereof.

9. The composition of claim 8, wherein said biologically active agent comprises human growth hormone.

10. The composition of claim 8, wherein said biologically active agent comprises interferon.

11. The composition of claim 8, wherein said biologically active agent comprises insulin.

12. The composition of claim 8, wherein said biologically active agent comprises heparin.

13. The composition of claim 8, wherein said biologically active agent comprises low molecular weight heparin.

14. The composition of claim 8, wherein said biologically active agent comprises cromolyn sodium.

15. The composition of claim 8, wherein said biologically active agent comprises PYY.

16. The composition of claim 8, wherein said biologically active agent comprises an anti-microbial agent.

17. The composition of claim 8, wherein said biologically active agent comprises calcitonin.

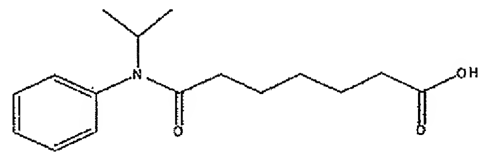
18. The composition of claim 8, wherein said biologically active agent comprises parathyroid hormone.

19. The composition of claim 8, wherein said biologically active agent comprises erythropoietin.

20. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal the composition of claim 2.

21. A compound selected from:

Compound 23



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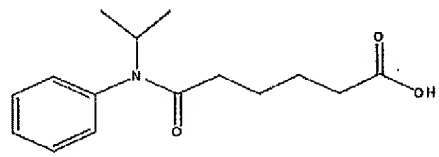

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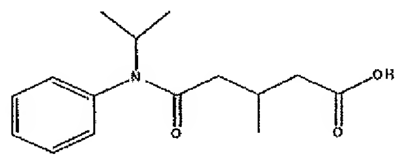

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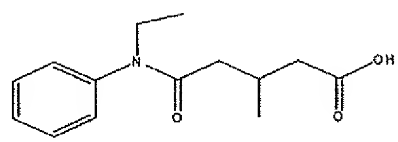

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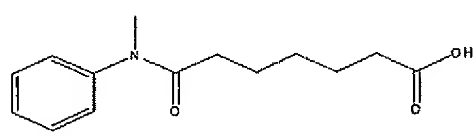

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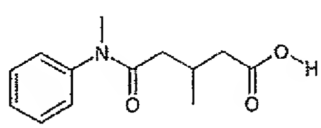

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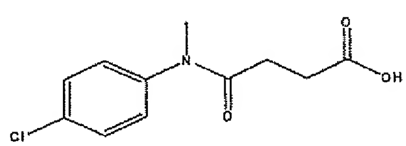

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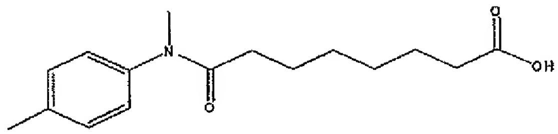

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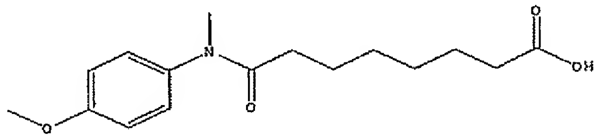

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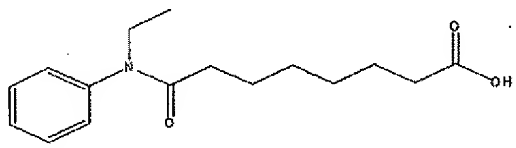

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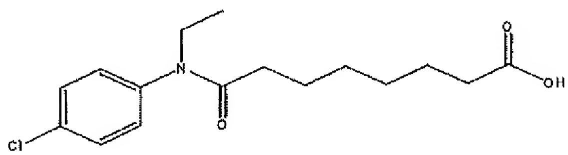

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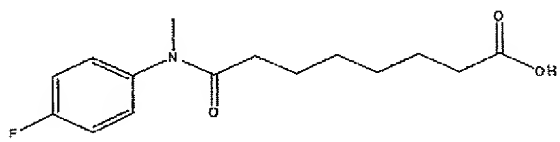

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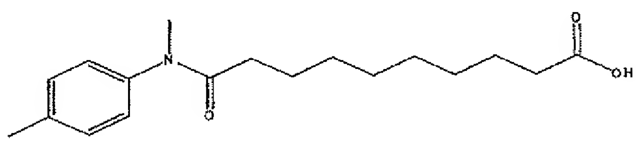

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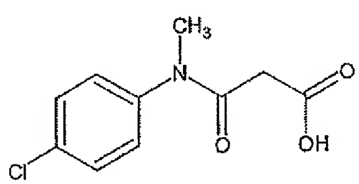

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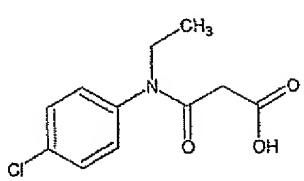

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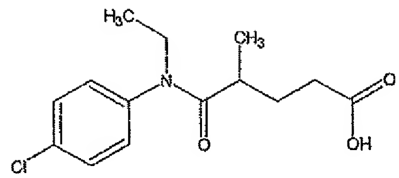

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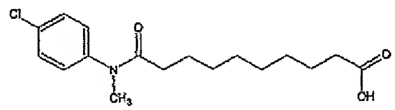

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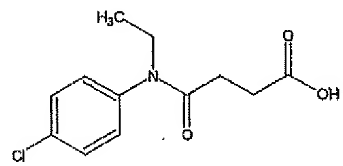

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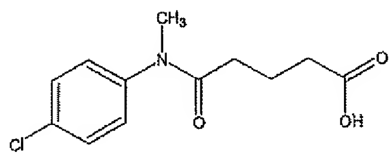

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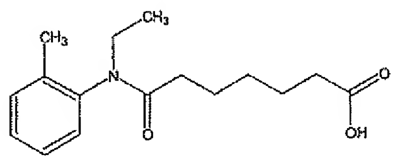
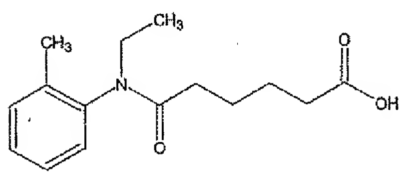


Compound 43



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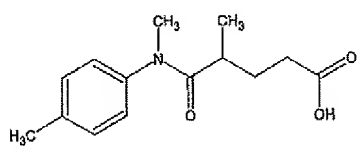

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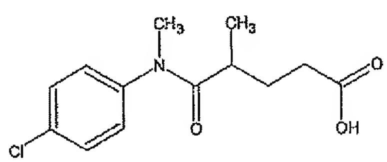

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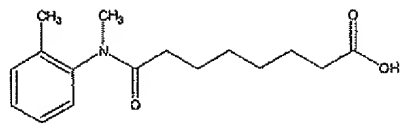

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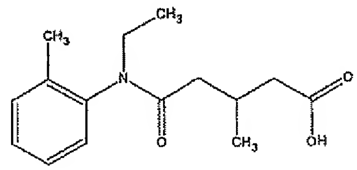

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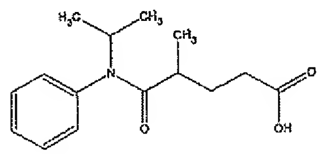

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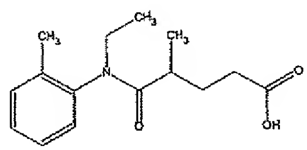

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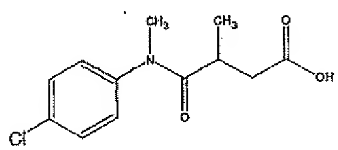

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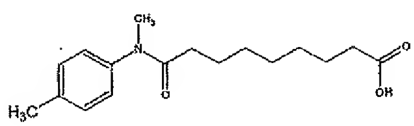

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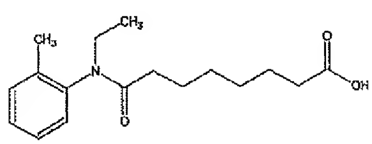

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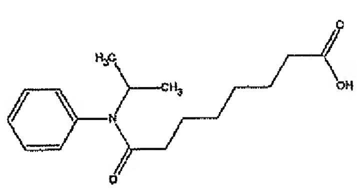
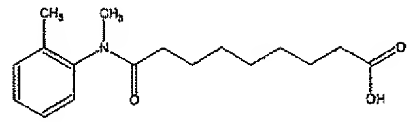
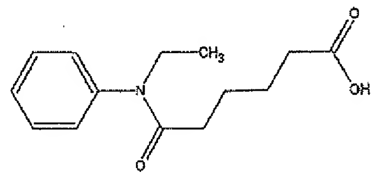
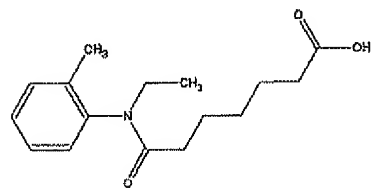
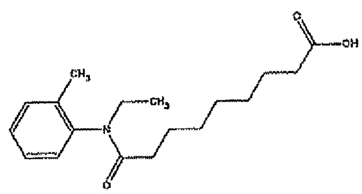
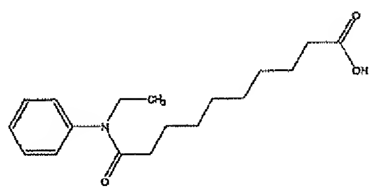


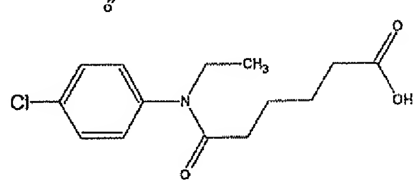
Compound 54 

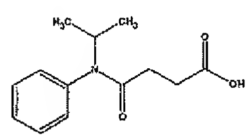
Compound 55 

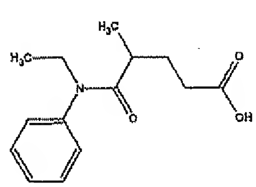
Compound 56 

Compound 57 

Compound 58 

Compound 59 

Compound 60 

Compound 61 

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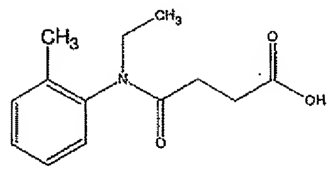

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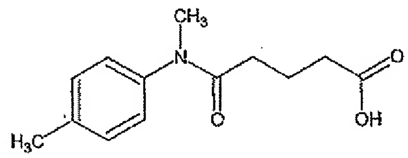

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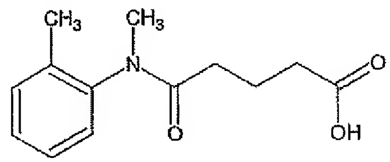

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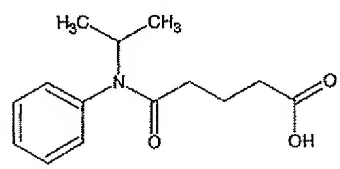

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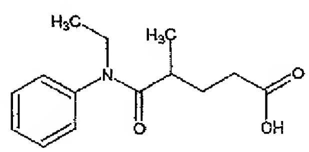

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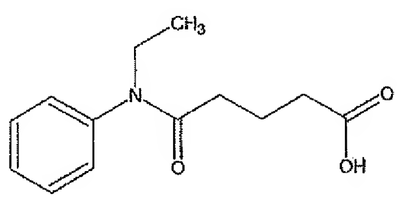

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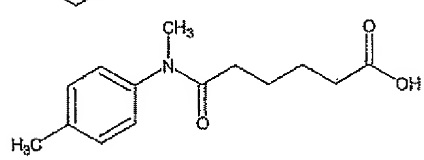

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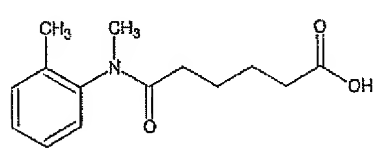

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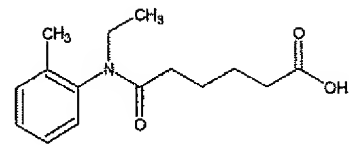

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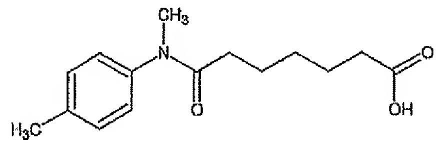

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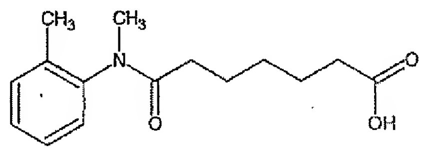

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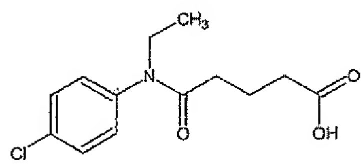

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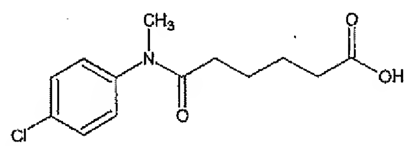

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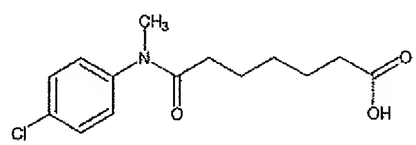

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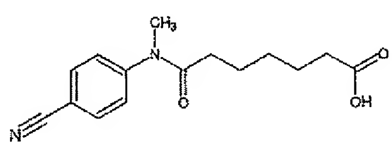

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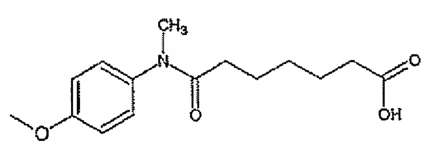

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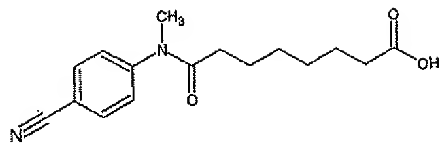

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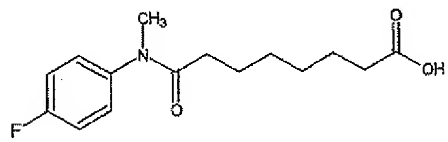

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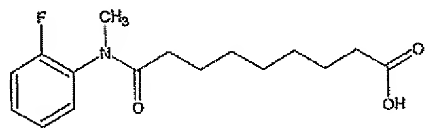

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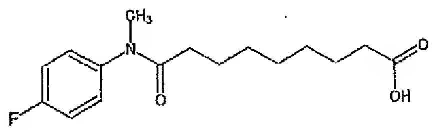

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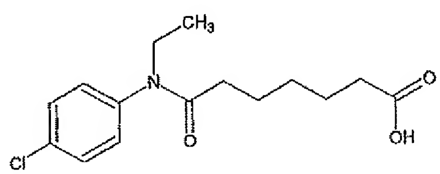

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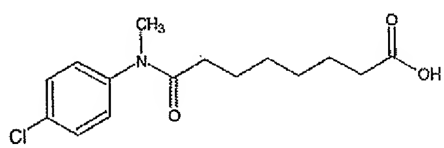

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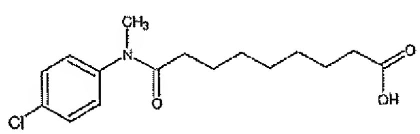

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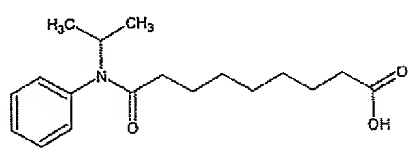

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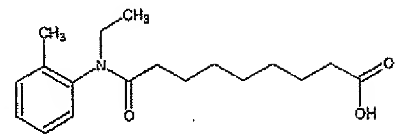

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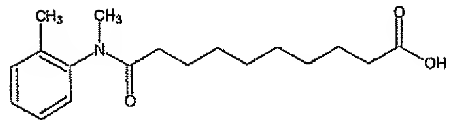

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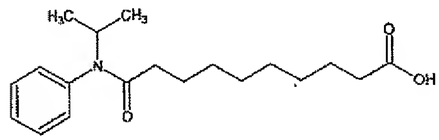

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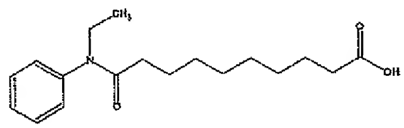

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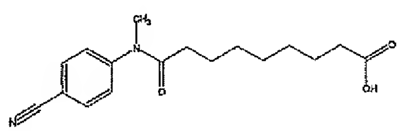

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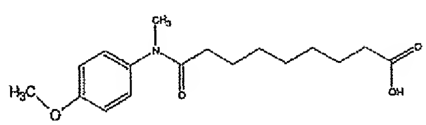

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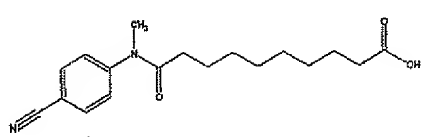

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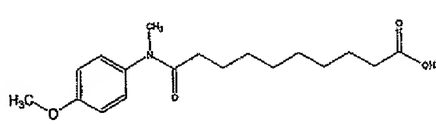

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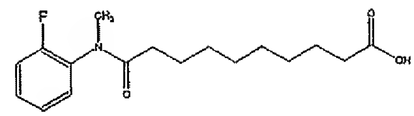

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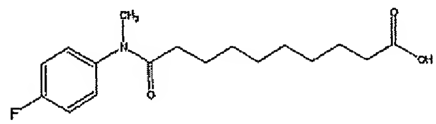

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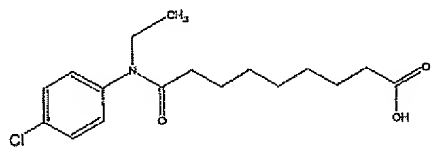

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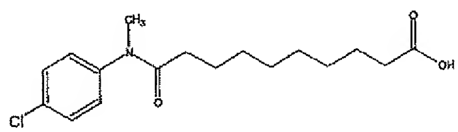

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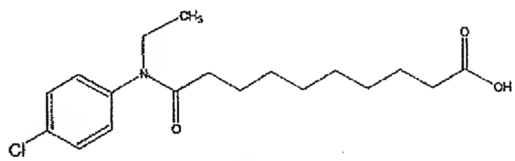

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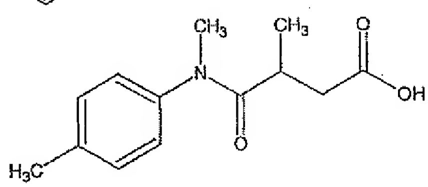

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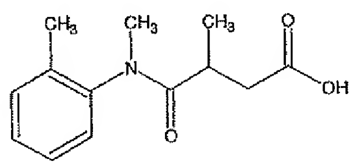

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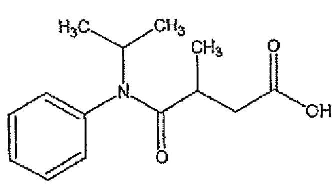

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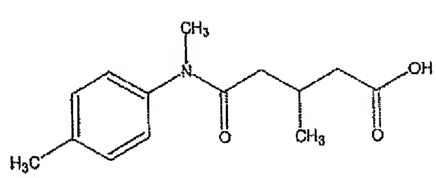
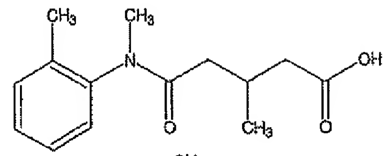
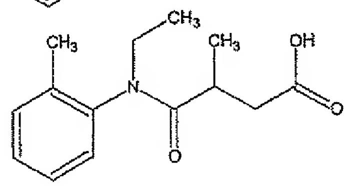
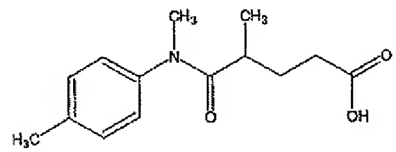
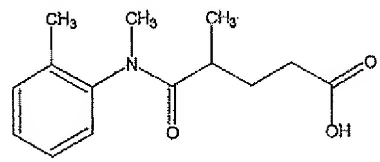
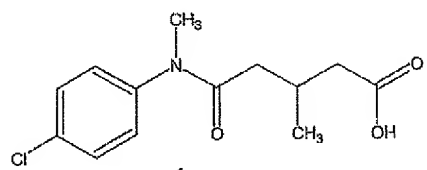


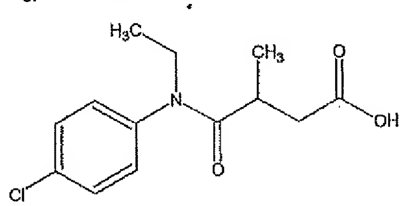
Compound 103 

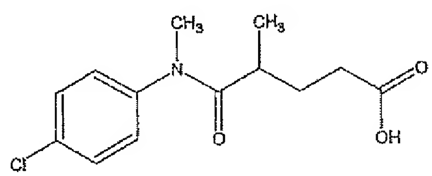
Compound 104 

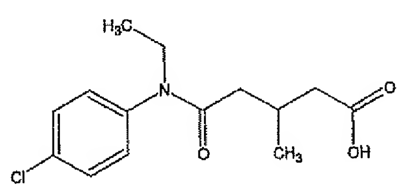
Compound 105 

Compound 106 

Compound 107 

Compound 108 

Compound 109 

Compound 110 

and salts thereof.

22. A composition comprising:

(A) at least one active agent; and

(B) a compound of claim 21.

22. The composition of claim 21, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

23. The composition of defined in claim 22, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

24. The composition of claim 22, wherein said biologically active agent is selected from the group consisting of

Amylin and Amylin Agonists;
Adrenocorticotropin;
Antigens;
Antimicrobials, including Antibiotics, Anti-Bacterials and Anti-Fungal Agents; non-limiting examples of Antibiotics include Gram-Positive Acting, Bacteriocidal, Lipopeptidal and Cyclic Peptidal Antibiotics, such as Daptomycin And Analogs thereof;
Anti-Migraine Agents such as BIBM-4096BS And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;
Antivirals including Acyclovir, Valacyclovir;
Atrial Naturetic Factor;
Bisphosphonates, including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;
Calcitonin, including Salmon, Eel, Porcine And Human;

Cholecystokinin (CCK) And CCK Agonists Including CCK-8;
Cromolyn Sodium (Sodium Or Disodium Chromoglycate);
Cyclosporine;
Desferrioxamine (DFO);
Erythropoietin;
Exedin and Exedin Agonists, including Exendin-3, Exendin-4;
Filgrastim
Follicle Stimulating Hormone (recombinant and natural);
Glucagon-Like Peptide 1 (GLP-1), Glucagon, and Glucagon-Like Peptide 2 (GLP-2);
Glucocerebrosidase;
Gonadotropin Releasing Hormone;
Growth Hormone Releasing Factor;
Growth Hormone Releasing Hormones;
Growth Hormones, Including Human Growth Hormones (hGH), Recombinant Human Growth Hormones (rhGH), Bovine Growth Hormones, And Porcine Growth Hormones;
Heparin, Including Unfractionated Heparin, Heparinoids, Dermatans, Chondroitins, Low Molecular Weight Heparin, Very Low Molecular Weight Heparin Ultra Low Molecular Weight Heparin and synthetic heparins including Fondiparinux;
Insulin, Including Porcine, Bovine, Human, And Human Recombinant, Optionally Having Counter Ions Including Zinc, Sodium, Calcium And Ammonium;
Insulin-Like Growth Factor, Including IGF-1;

Interferons, Including α (E.G., Interferon Alfacon-1 (Available As Infergen® From Intermune, Inc. Of Brisbane, Ca)), β, OMEGA and γ;
Interleukin-1; Interleukin-2; Interleukin-11; Interleukin-21;
Leutinizing Hormone and Leutinizing Hormone Releasing Hormone;
Leptin (OB Protein);
Monoclonal Antibodies including Retuxin, TNF-alpha soluble receptors;
Oxytocin;
Parathyroid Hormone (PTH), Including Its Fragments, including PTH 1-34 and PTH 1-38;
Peptide YY (PYY) Including PYY Agonists, Fragment 3-36;
Prostaglandins;
Protease Inhibitors;
Somatostatin;
Thrombopoietin;
Vancomycin;
Vasopressin;
Vitamins;
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;

or any combination thereof.

25. The composition of claim 24, wherein said biologically active agent comprises a human growth hormone, interferon, insulin, heparin, low molecular weight heparin, cromolyn sodium, PYY, an anti-microbial agent, calcitonin, parathyroid hormone, erythropoietin, and combinations thereof.

26. The composition of claim 25, wherein said biologically active agent comprises human growth hormone.

27. The composition of claim 25, wherein said biologically active agent comprises interferon.

28. The composition of claim 25, wherein said biologically active agent comprises insulin.

29. The composition of claim 25, wherein said biologically active agent comprises heparin.

30. The composition of claim 25, wherein said biologically active agent comprises low molecular weight heparin.

31. The composition of claim 25, wherein said biologically active agent comprises cromolyn sodium.

32. The composition of claim 25, wherein said biologically active agent comprises PYY.

33. The composition of claim 25, wherein said biologically active agent comprises an anti-microbial agent.

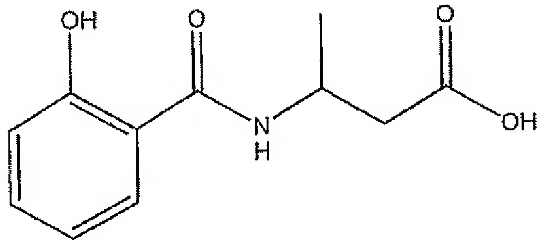
34. The composition of claim 25, wherein said biologically active agent comprises calcitonin.

35. The composition of claim 25, wherein said biologically active agent comprises parathyroid hormone.

36. The composition of claim 25, wherein said biologically active agent comprises erythropoietin.

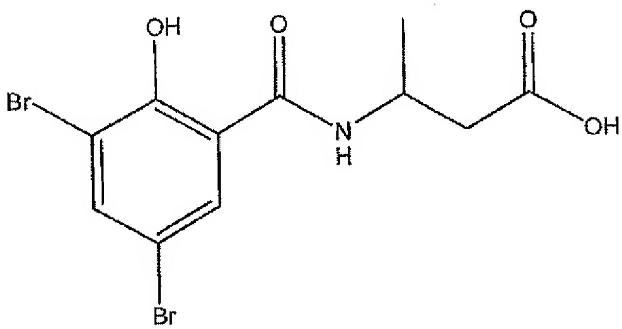
37. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal the composition of claim 22.

38. A compound selected from:



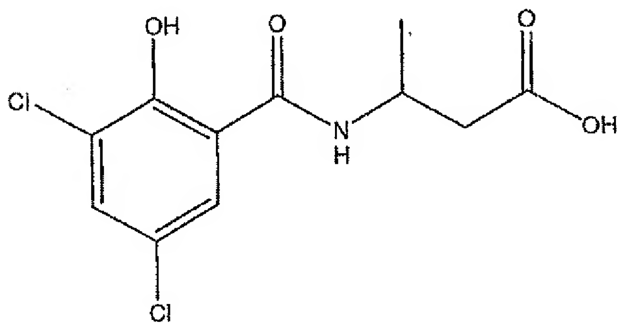
Compound 140

3-(2-Hydroxy-benzoylamino)-butyric acid



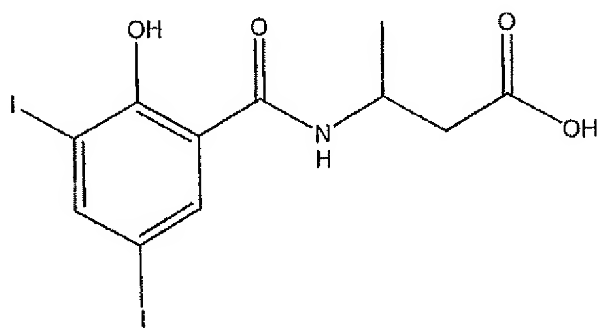
Compound 141

3-(3,5-Dibromo-2-hydroxy-benzoylamino)-butyric acid



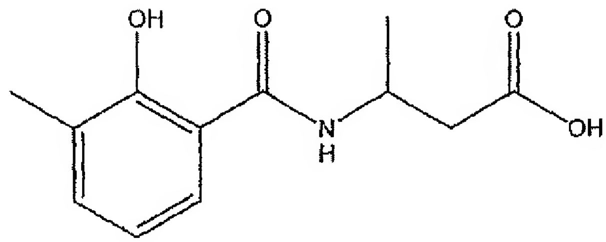
Compound 142

3-(3,5-Dichloro-2-hydroxy-benzoylamino)-butyric acid



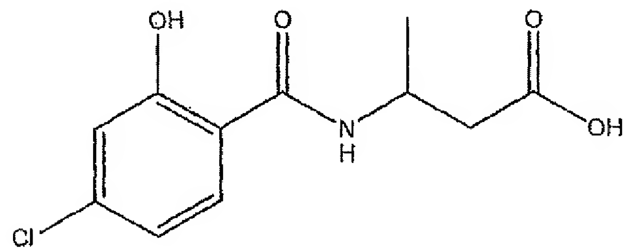
Compound 143

3-(2-Hydroxy-3,5-diiodo-benzoylamino)-butyric acid



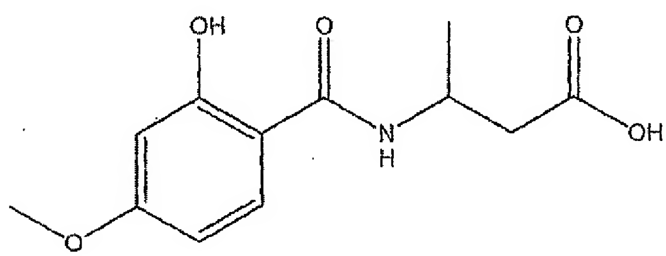
Compound 144

3-(2-Hydroxy-3-methyl-benzoylamino)-butyric acid



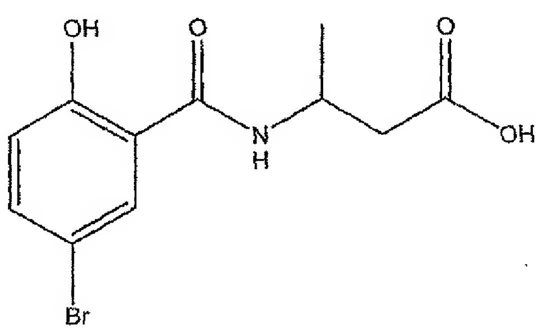
Compound 145

3-(4-Chloro-2-hydroxy-benzoylamino)-butyric acid



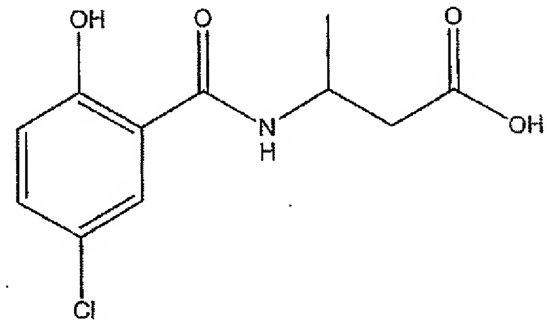
Compound 146

3-(2-Hydroxy-4-methoxy-benzoylamino)-butyric acid



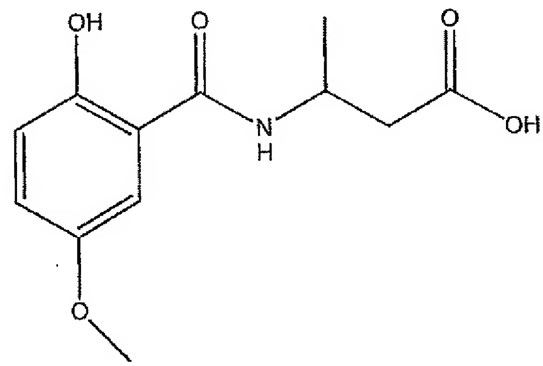
Compound 147

3-(5-Bromo-2-hydroxy-benzoylamino)-butyric acid



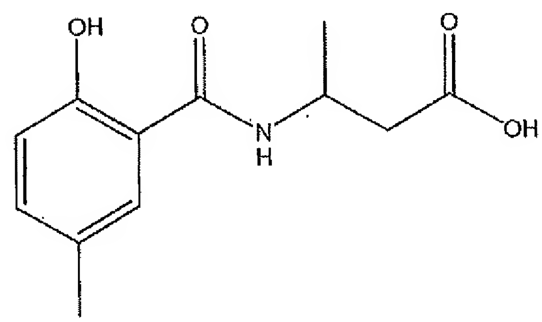
Compound 148

3-(5-Chloro-2-hydroxy-benzoylamino)-butyric acid



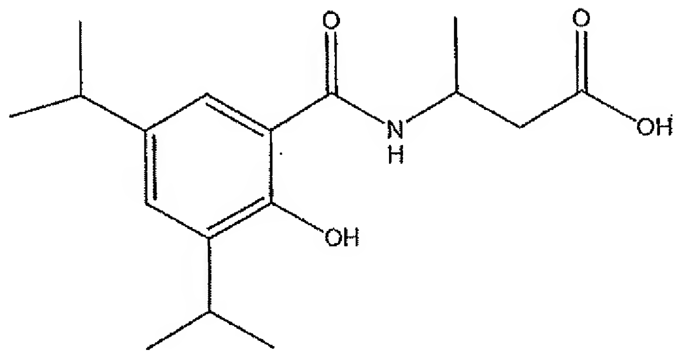
Compound 149

3-(2-Hydroxy-5-methoxy-benzoylamino)-butyric acid



Compound 150

3-(2-Hydroxy-5-methyl-benzoylamino)-butyric acid



Compound 151

3-(2-hydroxy-3,5-diisopropyl-benzoylamino)-butyric acid

and salts thereof.

39. A composition comprising:

(A) at least one active agent; and

(B) a compound of claim 38.

40. The composition of claim 39, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

41. The composition of defined in claim 40, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

42. The composition of claim 41, wherein said biologically active agent is selected from the group consisting of

Amylin and Amylin Agonists;
Adrenocorticotropin;
Antigens;

Antimicrobials, including Antibiotics, Anti-Bacterials and Anti-Fungal Agents; non-limiting examples of Antibiotics include Gram-Positive Acting, Bacteriocidal, Lipopeptidal and Cyclic Peptidal Antibiotics, such as Daptomycin And Analogs thereof;
Anti-Migraine Agents such as BIBM-4096BS And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;
Antivirals including Acyclovir, Valacyclovir;
Atrial Naturetic Factor;
Bisphosphonates, including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;
Calcitonin, including Salmon, Eel, Porcine And Human;
Cholecystokinin (CCK) And CCK Agonists Including CCK-8;
Cromolyn Sodium (Sodium Or Disodium Chromoglycate);
Cyclosporine;
Desferrioxamine (DFO);
Erythropoietin;
Exedin and Exedin Agonists, including Exendin-3, Exendin-4;
Filgrastim
Follicle Stimulating Hormone (recombinant and natural);
Glucagon-Like Peptide 1 (GLP-1), Glucagon, and Glucagon-Like Peptide 2 (GLP-2);
Glucocerebrosidase;
Gonadotropin Releasing Hormone;

Growth Hormone Releasing Factor;
Growth Hormone Releasing Hormones;
Growth Hormones, Including Human Growth Hormones (hGH), Recombinant Human Growth Hormones (rhGH), Bovine Growth Hormones, And Porcine Growth Hormones;
Heparin, Including Unfractionated Heparin, Heparinoids, Dermatans, Chondroitins, Low Molecular Weight Heparin, Very Low Molecular Weight Heparin Ultra Low Molecular Weight Heparin and synthetic heparins including Fondiparinux;
Insulin, Including Porcine, Bovine, Human, And Human Recombinant, Optionally Having Counter Ions Including Zinc, Sodium, Calcium And Ammonium;
Insulin-Like Growth Factor, Including IGF-1;
Interferons, Including α (E.G., Interferon Alfacon-1 (Available As Infergen® From Intermune, Inc. Of Brisbane, Ca)), β, OMEGA and γ;
Interleukin-1; Interleukin-2; Interleukin-11; Interleukin-21;
Leutinizing Hormone and Leutinizing Hormone Releasing Hormone;
Leptin (OB Protein);
Monoclonal Antibodies including Retuxin, TNF-alpha soluble receptors;
Oxytocin;
Parathyroid Hormone (PTH), Including Its Fragments, including PTH 1-34 and PTH 1-38;
Peptide YY (PYY) Including PYY Agonists, Fragment 3-36;
Prostaglandins;
Protease Inhibitors;

Somatostatin;
Thrombopoietin;
Vancomycin;
Vasopressin;
Vitamins;
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;

or any combination thereof.

43. The composition of claim 42, wherein said biologically active agent comprises human growth hormone.

44. The composition of claim 42, wherein said biologically active agent comprises interferon.

45. The composition of claim 42, wherein said biologically active agent comprises insulin.

46. The composition of claim 42, wherein said biologically active agent comprises heparin.

47. The composition of claim 42, wherein said biologically active agent comprises cromolyn sodium.

48. The composition of claim 42, wherein said biologically active agent comprises PYY.

49. The composition of claim 42, wherein said biologically active agent comprises an anti-microbial agent.

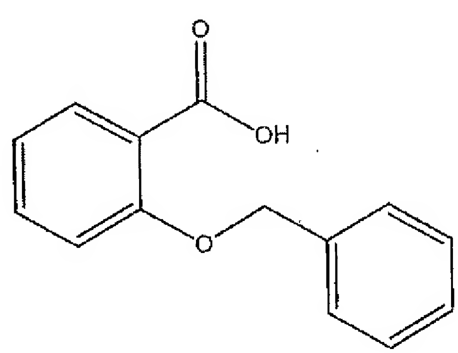
50. The composition of claim 42, wherein said biologically active agent comprises calcitonin.

51. The composition of claim 42, wherein said biologically active agent comprises parathyroid hormone.

52. The composition of claim 42, wherein said biologically active agent comprises erythropoietin.

53. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal the composition of claim 39.

54. A compound comprising:



Compound 159

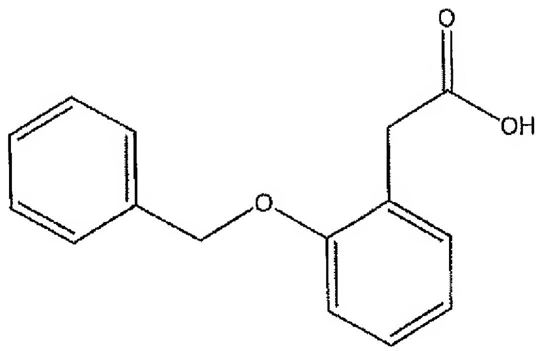
2-Benzyloxybenzoic acid

and salts thereof.

55. A composition comprising:

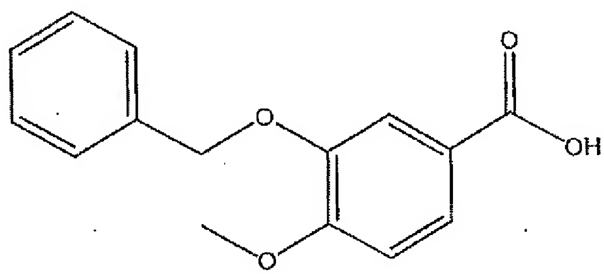
(A) at least one active agent; and

(B) a compound selected from



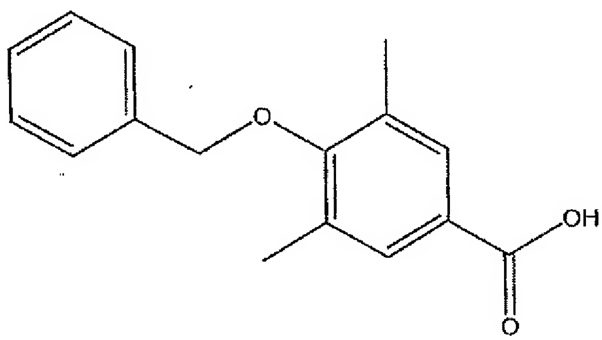
Compound 152

2-Benzyloxyphenyl acetic acid



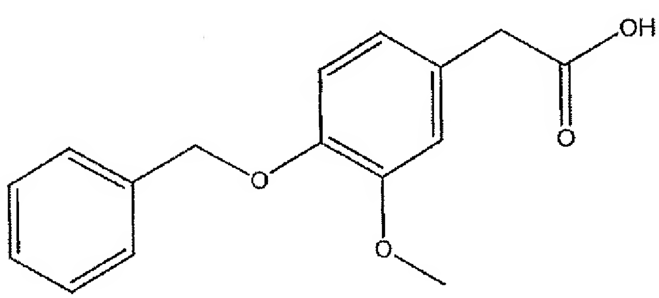
Compound 153

3-Benzyloxy-4-methoxybenzoic acid



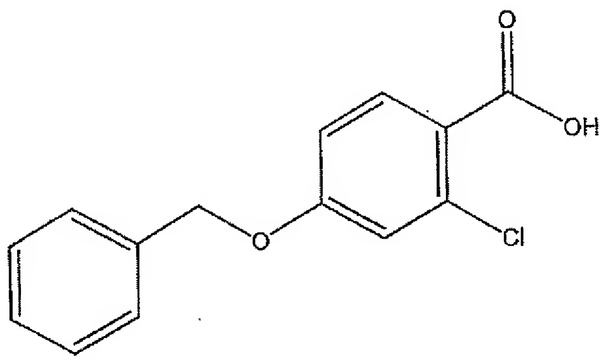
Compound 154

4-Benzyloxy-3,5-dimethylbenzoic acid



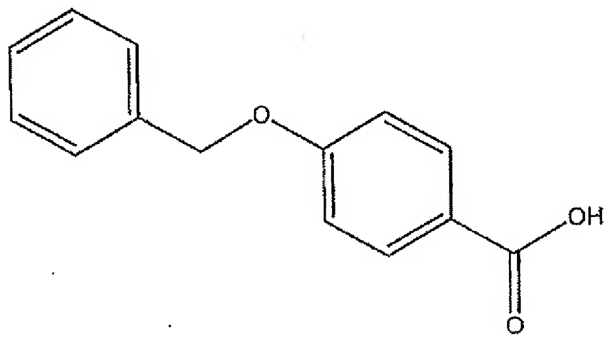
Compound 155

(4-Benzyloxy-3-methoxy-phenyl)-acetic acid



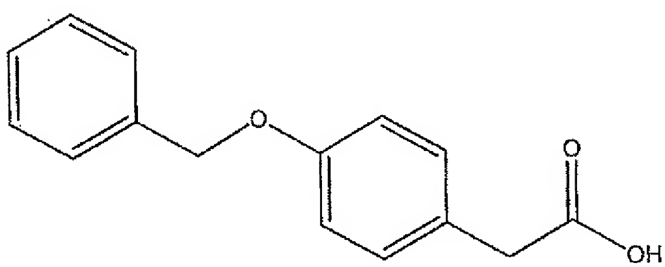
Compound 156

4-(Benzyloxy)-2-chlorobenzoic acid



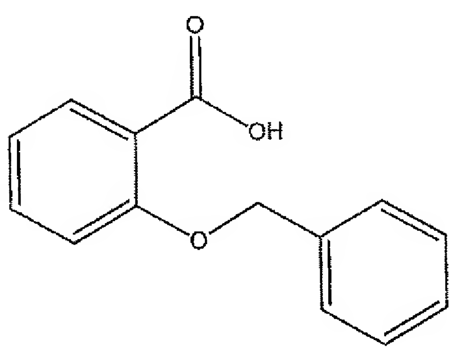
Compound 157

4-Benzyloxy-benzoic acid



Compound 158

(4-Benzyloxy-phenyl)-acetic acid



Compound 159

2-Benzyloxybenzoic acid

and salts thereof.

56. The composition of claim 55, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

57. The composition of defined in claim 56, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

58. The composition of claim 57, wherein said biologically active agent is selected from the group consisting of

Amylin and Amylin Agonists;
Adrenocorticotropin;
Antigens;
Antimicrobials, including Antibiotics, Anti-Bacterials and Anti-Fungal Agents; non-limiting examples of Antibiotics include Gram-Positive Acting, Bacteriocidal, Lipopeptidal and Cyclic Peptidal Antibiotics, such as Daptomycin And Analogs thereof;
Anti-Migraine Agents such as BIBM-4096BS And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;
Antivirals including Acyclovir, Valacyclovir;
Atrial Naturetic Factor;
Bisphosphonates, including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;
Calcitonin, including Salmon, Eel, Porcine And Human;

Cholecystokinin (CCK) And CCK Agonists Including CCK-8;
Cromolyn Sodium (Sodium Or Disodium Chromoglycate);
Cyclosporine;
Desferrioxamine (DFO);
Erythropoietin;
Exedin and Exedin Agonists, including Exendin-3, Exendin-4;
Filgrastim
Follicle Stimulating Hormone (recombinant and natural);
Glucagon-Like Peptide 1 (GLP-1), Glucagon, and Glucagon-Like Peptide 2 (GLP-2);
Glucocerebrosidase;
Gonadotropin Releasing Hormone;
Growth Hormone Releasing Factor;
Growth Hormone Releasing Hormones;
Growth Hormones, Including Human Growth Hormones (hGH), Recombinant Human Growth Hormones (rhGH), Bovine Growth Hormones, And Porcine Growth Hormones;
Heparin, Including Unfractionated Heparin, Heparinoids, Dermatans, Chondroitins, Low Molecular Weight Heparin, Very Low Molecular Weight Heparin Ultra Low Molecular Weight Heparin and synthetic heparins including Fondiparinux;
Insulin, Including Porcine, Bovine, Human, And Human Recombinant, Optionally Having Counter Ions Including Zinc, Sodium, Calcium And Ammonium;
Insulin-Like Growth Factor, Including IGF-1;

Interferons, Including α (E.G., Interferon Alfacon-1 (Available As Infergen® From Intermune, Inc. Of Brisbane, Ca)), β, OMEGA and γ;
Interleukin-1; Interleukin-2; Interleukin-11; Interleukin-21;
Leutinizing Hormone and Leutinizing Hormone Releasing Hormone;
Leptin (OB Protein);
Monoclonal Antibodies including Retuxin, TNF-alpha soluble receptors;
Oxytocin;
Parathyroid Hormone (PTH), Including Its Fragments, including PTH 1-34 and PTH 1-38;
Peptide YY (PYY) Including PYY Agonists, Fragment 3-36;
Prostaglandins;
Protease Inhibitors;
Somatostatin;
Thrombopoietin;
Vancomycin;
Vasopressin;
Vitamins;
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;

or any combination thereof.

59. The composition of claim 58, wherein said biologically active agent comprises human growth hormone.

60. The composition of claim 58, wherein said biologically active agent comprises interferon.

61. The composition of claim 58, wherein said biologically active agent comprises insulin.

62. The composition of claim 58, wherein said biologically active agent comprises heparin.

63. The composition of claim 58, wherein said biologically active agent comprises low molecular weight heparin.

64. The composition of claim 58, wherein said biologically active agent comprises cromolyn sodium.

65. The composition of claim 58, wherein said biologically active agent comprises PYY.

66. The composition of claim 58, wherein said biologically active agent comprises an anti-microbial agent.

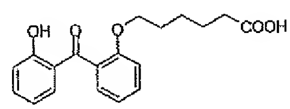
67. The composition of claim 58, wherein said biologically active agent comprises calcitonin.

68. The composition of claim 58, wherein said biologically active agent comprises parathyroid hormone.

69. The composition of claim 58, wherein said biologically active agent comprises erythropoietin.

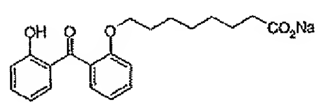
70. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal the composition of claim 56.

71. A compound comprising:



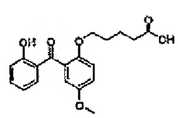
Compound 160

6-(2-(2-Hydroxybenzoyl)phenoxy)hexanoic acid



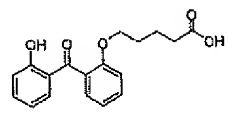
Compound 161

Sodium 8-(2-(2-Hydroxybenzoyl)phenoxy)octanoate



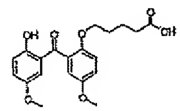
Compound 162

5-(2-(2-Hydroxybenzoyl)-4-methoxyphenoxy)valeric acid



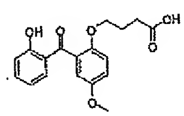
Compound 163

5-(2-(2-Hydroxybenzoyl)phenoxy)valeric acid



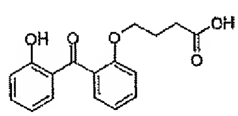
Compound 164

5-(2-(2-Hydroxy-5-methoxybenzoyl)-4-methoxyphenoxy) valeric acid



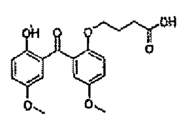
Compound 165

4-(2-(2-Hydroxybenzoyl)-5-methoxyphenoxy)butyric acid



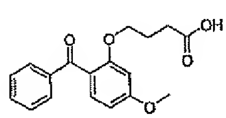
Compound 166

4-(2-(2-Hydroxybenzoyl)phenoxy)butyric



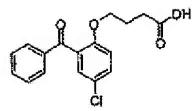
Compound 167

4-(2-Chlorobenzoyl-4-methylphenoxy)butyric acid



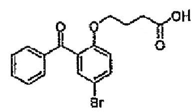
Compound 168

4-(2-Benzoyl-5-methoxyphenoxy)butyric



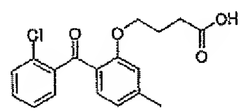
Compound 169

4-(2-Benzoyl-4-chlorophenoxy)butyric acid



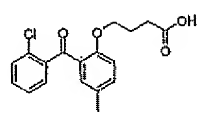
Compound 170

4-(2-Benzoyl-4-bromophenoxy)butyric acid



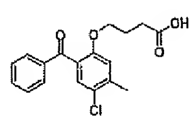
Compound 171

4-(2-(2-Chlorobenzoyl-5-methylphenoxy)butyric acid



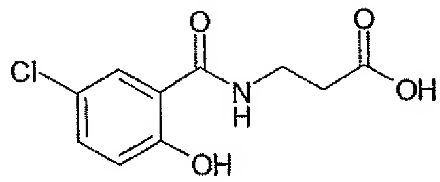
Compound 172

4-(2-(2-Chlorobenzoyl-4-methylphenoxy)butyric acid



Compound 173

4-(2-Benzoyl-4-chloro-5-methylphenoxy)butyric acid



Compound 174

and salts thereof.

72. A composition comprising:

(A) at least one active agent; and

(B) a compound of claim 71.

73. The composition of claim 72, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

74. The composition of defined in claim 72, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

75. The composition of claim 72, wherein said biologically active agent is selected from the group consisting of

Amylin and Amylin Agonists;
Adrenocorticotropin;
Antigens;
Antimicrobials, including Antibiotics, Anti-Bacterials and Anti-Fungal Agents; non-limiting examples of Antibiotics include Gram-Positive Acting, Bacteriocidal, Lipopeptidal and Cyclic Peptidal Antibiotics, such as Daptomycin And Analogs thereof;
Anti-Migraine Agents such as BIBM-4096BS And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;
Antivirals including Acyclovir, Valacyclovir;

Atrial Naturetic Factor;
Bisphosphonates, including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;
Calcitonin, including Salmon, Eel, Porcine And Human;
Cholecystokinin (CCK) And CCK Agonists Including CCK-8;
Cromolyn Sodium (Sodium Or Disodium Chromoglycate);
Cyclosporine;
Desferrioxamine (DFO);
Erythropoietin;
Exedin and Exedin Agonists, including Exendin-3, Exendin-4;
Filgrastim
Follicle Stimulating Hormone (recombinant and natural);
Glucagon-Like Peptide 1 (GLP-1), Glucagon, and Glucagon-Like Peptide 2 (GLP-2);
Glucocerebrosidase;
Gonadotropin Releasing Hormone;
Growth Hormone Releasing Factor;
Growth Hormone Releasing Hormones;
Growth Hormones, Including Human Growth Hormones (hGH), Recombinant Human Growth Hormones (rhGH), Bovine Growth Hormones, And Porcine Growth Hormones;

Heparin, Including Unfractionated Heparin, Heparinoids, Dermatans, Chondroitins, Low Molecular Weight Heparin, Very Low Molecular Weight Heparin Ultra Low Molecular Weight Heparin and synthetic heparins including Fondiparinux;
Insulin, Including Porcine, Bovine, Human, And Human Recombinant, Optionally Having Counter Ions Including Zinc, Sodium, Calcium And Ammonium;
Insulin-Like Growth Factor, Including IGF-1;
Interferons, Including α (E.G., Interferon Alfacon-1 (Available As Infergen® From Intermune, Inc. Of Brisbane, Ca)), β, OMEGA and γ;
Interleukin-1; Interleukin-2; Interleukin-11; Interleukin-21;
Leutinizing Hormone and Leutinizing Hormone Releasing Hormone;
Leptin (OB Protein);
Monoclonal Antibodies including Retuxin, TNF-alpha soluble receptors;
Oxytocin;
Parathyroid Hormone (PTH), Including Its Fragments, including PTH 1-34 and PTH 1-38;
Peptide YY (PYY) Including PYY Agonists, Fragment 3-36;
Prostaglandins;
Protease Inhibitors;
Somatostatin;
Thrombopoietin;
Vancomycin;
Vasopressin;

Vitamins;
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;

or any combination thereof.

76. The composition of claim 75, wherein said biologically active agent comprises human growth hormone.

77. The composition of claim 75, wherein said biologically active agent comprises interferon.

78. The composition of claim 75, wherein said biologically active agent comprises insulin.

79. The composition of claim 75, wherein said biologically active agent comprises heparin.

80. The composition of claim 75, wherein said biologically active agent comprises low molecular weight heparin.

81. The composition of claim 75, wherein said biologically active agent comprises cromolyn sodium.

82. The composition of claim 75, wherein said biologically active agent comprises PYY.

83. The composition of claim 75, wherein said biologically active agent comprises an anti-microbial agent.

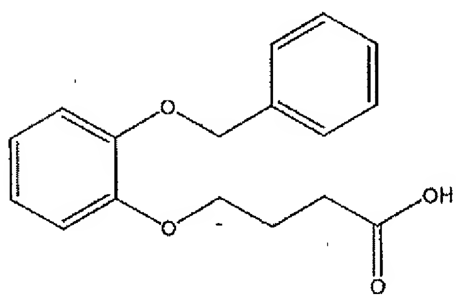
84. The composition of claim 75, wherein said biologically active agent comprises calcitonin.

85. The composition of claim 75, wherein said biologically active agent comprises parathyroid hormone.

86. The composition of claim 75, wherein said biologically active agent comprises erythropoietin.

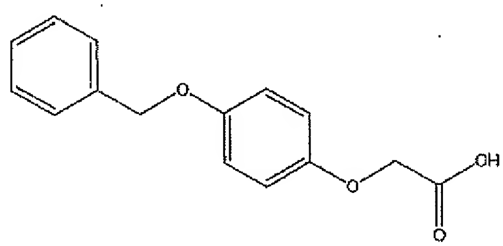
87. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal the composition of claim 72.

88. A compound selected from:



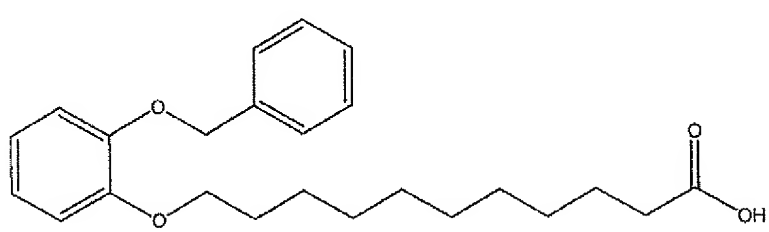
Compound 175

4-(2-Benzyloxy-phenoxy)-butyric acid



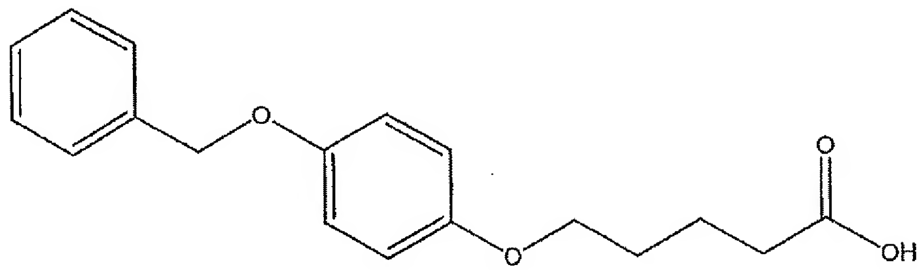
Compound 176

(4-Benzyloxy-phenoxy)-acetic acid



Compound 177

11-(2-Benzyloxyphenoxy)undecanoic acid



Compound 178

5-(4-Benzyloxy-phenoxy)-pentanoic acid

or a salt thereof.

89. A composition comprising:

(A) at least one active agent; and

(B) a compound of claim 88.

90. The composition of claim 89, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

91. The composition of claim 89, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

92. The composition of claim 89, wherein said biologically active agent is selected from the group consisting of

Amylin and Amylin Agonists;
Adrenocorticotropin;
Antigens;
Antimicrobials, including Antibiotics, Anti-Bacterials and Anti-Fungal Agents; non-limiting examples of Antibiotics include Gram-Positive Acting, Bacteriocidal, Lipopeptidal and Cyclic Peptidal Antibiotics, such as Daptomycin And Analogs thereof;

Anti-Migraine Agents such as BIBM-4096BS And Other Calcitonin Gene-Related Proteins Antagonists, Sumatriptan Succinate;
Antivirals including Acyclovir, Valacyclovir;
Atrial Naturetic Factor;
Bisphosphonates, including Alendronate, Clodronate, Etidronate, Ibandronate, Incadronate, Minodronate, Neridronate, Olpadronate, Pamidronate, Risedronate, Tiludronate, Zoledronate, EB1053, and YH529;
Calcitonin, including Salmon, Eel, Porcine And Human;
Cholecystokinin (CCK) And CCK Agonists Including CCK-8;
Cromolyn Sodium (Sodium Or Disodium Chromoglycate);
Cyclosporine;
Desferrioxamine (DFO);
Erythropoietin;
Exedin and Exedin Agonists, including Exendin-3, Exendin-4;
Filgrastim
Follicle Stimulating Hormone (recombinant and natural);
Glucagon-Like Peptide 1 (GLP-1), Glucagon, and Glucagon-Like Peptide 2 (GLP-2);
Glucocerebrosidase;
Gonadotropin Releasing Hormone;
Growth Hormone Releasing Factor;
Growth Hormone Releasing Hormones;

Growth Hormones, Including Human Growth Hormones (hGH), Recombinant Human Growth Hormones (rhGH), Bovine Growth Hormones, And Porcine Growth Hormones;
Heparin, Including Unfractionated Heparin, Heparinoids, Dermatans, Chondroitins, Low Molecular Weight Heparin, Very Low Molecular Weight Heparin Ultra Low Molecular Weight Heparin and synthetic heparins including Fondiparinux;
Insulin, Including Porcine, Bovine, Human, And Human Recombinant, Optionally Having Counter Ions Including Zinc, Sodium, Calcium And Ammonium;
Insulin-Like Growth Factor, Including IGF-1;
Interferons, Including α (E.G., Interferon Alfacon-1 (Available As Infergen® From Intermune, Inc. Of Brisbane, Ca)), β, OMEGA and γ;
Interleukin-1; Interleukin-2; Interleukin-11; Interleukin-21;
Leutinizing Hormone and Leutinizing Hormone Releasing Hormone;
Leptin (OB Protein);
Monoclonal Antibodies including Retuxin, TNF-alpha soluble receptors;
Oxytocin;
Parathyroid Hormone (PTH), Including Its Fragments, including PTH 1-34 and PTH 1-38;
Peptide YY (PYY) Including PYY Agonists, Fragment 3-36;
Prostaglandins;
Protease Inhibitors;
Somatostatin;
Thrombopoietin;

Vancomycin;
Vasopressin;
Vitamins;
Vaccines Including Those Against Anthrax Or Y. Pestis, Influenza, and Herpes;

or any combination thereof.

93. The composition of claim 92, wherein said biologically active agent comprises human growth hormone.

94. The composition of claim 92, wherein said biologically active agent comprises interferon.

95. The composition of claim 92, wherein said biologically active agent comprises insulin.

96. The composition of claim 92, wherein said biologically active agent comprises heparin.

97. The composition of claim 92, wherein said biologically active agent comprises low molecular weight heparin.

98. The composition of claim 92, wherein said biologically active agent comprises cromolyn sodium.

99. The composition of claim 92, wherein said biologically active agent comprises PYY.

100. The composition of claim 92, wherein said biologically active agent comprises an anti-microbial agent.

101. The composition of claim 92, wherein said biologically active agent comprises calcitonin.

102. The composition of claim 92, wherein said biologically active agent comprises parathyroid hormone.

103. The composition of claim 92, wherein said biologically active agent comprises erythropoietin.

104. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal the composition of claim 89.